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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

FEBRUARY, 1944

ORIGINAL ARTICLES

OSTEOSCLEROSIS, MYELOFIBROSIS AND LEUKEMIA

By Jacob Churg, M.D.
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(From the Laboratories of the Mt. Sinai Hospital)

Osteodystrophic changes in the bones such as osteosclerosis and fibrosis of bone marrow may be accompanied by a disturbance of the white blood cell picture, characterized by a high count and the appearance of immature elements in the circulation, as well as by leukopenia and anemia. Because of the blood changes, as well as splenomegaly and progressive fatal course, the first observers[2,7,18,19] regarded such cases as instances of true leukemia, or at least, very closely allied with the latter condition. "Osteosclerotic leukemia" merits a special section in Henke-Lubarsch's Handbook of Pathology.[6] However, more recently, there has appeared a tendency to separate all these cases from leukemia and to place them in a different group, known under a variety of names, such as chronic non-leukemic myelosis,[14] megakaryocytic myeloid splenomegaly,[4] leuko-erythroblastic anemia,[21] and so on. The non-leukemic myelosis is similar to leukemia in many of its clinical and pathologic aspects, but has been adequately differentiated from the latter condition and established as an independent entity by recent investigations.[3,8,10] As all reports indicate[3,10,20] the non-leukemic myelosis is frequently associated with osteodystrophic changes. It seems important, however, to determine, especially from the prognostic standpoint, whether such changes do not also occur in leukemia. For that purpose, we have reëxamined, paying special attention to the changes in the bone marrow, all cases in our laboratory which in the last 10 years were diagnosed as leukemia on postmortem examination. It must be mentioned, however, that possible instances of non-leukemic myelosis might have been included under this heading.

Among our material, there were 82 cases of myeloid leukemia—46 of the acute or subacute, and 36 of the chronic variety, as well as 15 cases of lymphatic leukemia. Of these 97, 7 showed considerable or even pronounced osteodystrophic changes—2 in the subacute myeloid

group and 5 in the chronic myeloid. The subacute cases did not receive any specific therapy, whereas the chronic cases were subjected to radiation in varying amounts. Only 2 cases of the latter group are presented below; the other 3 showed changes very similar to those found in Case 3, and are therefore omitted for the sake of brevity.

Case Studies. CASE 1. J. D., white, male, age 18; No. 486191 (P. M. 12128). The patient was admitted to the Mount Sinai Hospital in July 1941, complaining of severe low back pain and fever. He was well developed for his age. There were no significant physical findings except for a moderate generalized enlargement of the lymph nodes. The blood count showed: Hgb. 80%, R.B.C. 4.12 mill.; W.B.C. 4650 (neutrophils 56%, lymphocytes 42%, monocytes 2%), no abnormal cells in the smear. Enteric fever and infectious mononucleosis were considered, but the temperature dropped promptly, the pain subsided, and the patient was discharged with the diagnosis of the grippe. He was readmitted in 5 weeks with pain in the left chest and fever. The enlargement of the lymph nodes was more prominent, the spleen and liver became palpable while under observation. The blood count revealed: Hgb. 62%, R.B.C. 3.07 mill., W.B.C. 4050 (myeloblasts 8%, non-segmented neutrophils 11%, segmented 20%, lymphocytes 54%, monocytes 4%, eosinophils 2%, plasma cells 1%, normoblasts 2 per 100 W.B.C.), platelets 40,000. Sternal aspiration showed an almost completely myeloblastic bone marrow, thus establishing the diagnosis of myeloblastic leukemia. Roentgen ray examination of the ribs was entirely negative. The Wassermann reaction gave negative results on repeated occasions.

From September 1941 until the time of his death in March 1942, the patient was under observation in the hospital and in the hematology clinic. His white count always remained low, sometimes dropping to 700 and never rising above 13,000. In October 1941 the blood count was as follows: Hgb. 58%, R.B.C. 3.0 mill., W.B.C. 7300 (myeloblasts 44%, promyeloblasts 1%, myelocytes 3%, non-segmented neutrophils 5%, segmented 4%, lymphocytes 36%, monocytes 3%, eosinophils 1%, 6 normoblasts and 1 erythroblast per 100 W.B.C.). The patient was sustained by repeated blood transfusions, yet his hemoglobin continued to drop, especially during the numerous febrile episodes. He developed left purulent otitis media and mastoiditis which were temporarily held in check by sulfonamides, but eventually flared up and apparently became the starting point of the terminal sepsis. On his last admission his Hgb. was 23%, W.B.C. 800 (20% myeloblasts, 1% myelocytes, 2% non-segmented neutrophils, 14% segmented, 62% lymphocytes and 1% monocytes). In spite of sulfathiazole administration, the temperature rose to 106° F. and the patient died 8 months after the onset of first symptoms.

Autopsy (5 hours after death). Only pertinent findings are recorded. The body was pale and emaciated. Numerous petechiæ were found over the trunk and extremities; the gums were covered with clotted blood.

Heart: Dilated, very flabby and pale. The myocardium showed diffuse yellowish mottling caused by focal fatty changes in the muscle. *Microscopic* collections of myeloid cells were found within the epicardium.

Lungs contained scattered and confluent areas of bronchopneumonia, especially numerous in both lower lobes. These areas were slightly raised, dry, and varied in color from gray to dark red. Several pinhead-size abscesses were found in the right upper lobe. The hilar lymph nodes were moderately enlarged, soft and anthracotic. *Microscopically*, the alveoli within the pneumonic areas were filled with fibrin together with a varying admixture of red cells and young myeloid cells but very few polymorphonuclears. There were many small focal collections of myeloid cells around the bronchi.

Liver weighed 2360 gm. The capsule was smooth and brown in color. Under the capsule and throughout the parenchyma, there were scattered numerous pinhead-sized abscesses filled with creamy yellowish pus. The lobular architecture of the liver was blurred, though there were many grayish dots and

streaks which seemed to correspond with the periportal areas. *Microscopically*, there was distinct cellular infiltration of the periportal fields, many of which were considerably enlarged. In addition to lymphocytes, there were also numerous, young myeloid cells (myeloblasts and myelocytes). The sinusoids were congested, but otherwise not involved. The Kupffer cells were prominent. The abscesses were often surrounded by collections of myeloid cells and small cells with dark nuclei and scanty cytoplasm, either lymphocytes or atypical myeloblasts. There were no megakaryocytes or erythroblasts. Numerous granules of hemosiderin were found both within and outside of the liver cells.

Spleen: Large (weight 600 gm.). Several yellowish white infarcts were observed near the upper pole. On section, the cut surface was moderately firm and dark red in color. The trabeculæ were distinct. The Malpighian corpuscles were fairly numerous but very small. Under the *microscope* it could be seen that the architecture was rather well preserved, though both the red and the white pulp were infiltrated with very young myeloid cells. The infiltration was focal rather than diffuse and especially prominent in the perifollicular zones. Often the foci of infiltration consisted of small groups of large, very immature cells with large vesicular nuclei surrounded by smaller myeloblasts and myelocytes. In addition to the myeloid cells there was a fair number of scattered megakaryocytes and small nests of erythroblasts. Hemosiderin was found in large quantities, both intracellular and extracellular.

Lymph nodes, including the periaortic, peripancreatic, portal and mesenteric, were large measuring up to 2 cm. in diameter. They were soft in consistency and pinkish red in color. The cut surface had a homogenous reddish gray appearance. *Microscopically*, all of the examined lymph nodes showed a diffuse myeloid metaplasia with more or less pronounced obliteration of the normal architecture. There were no erythroblasts or megakaryocytes.

Bone Marrow: Because of the limited permission, only the vertebral column was examined. The bony trabeculation was distinct throughout. The marrow was red and moist but in many areas it appeared pale, dry, and grayish in color. *Microscopic* sections at different levels showed a somewhat varying picture (Figs. 1 and 2). In general, there was a widening of the trabeculæ, but the intertrabecular spaces did not appear to be narrowed. The normal marrow had completely disappeared. In most of the sections it was replaced by very loose connective tissue surrounding wide vascular spaces. Within the meshes of the connective tissue, there was found a small number of myeloid cells, occasional erythroblasts and, very rarely, megakaryocytes. In places, the meshes were filled with pinkish stained homogenous material. In other sections, the process of marrow replacement appeared to have progressed further than in the previous case. The vascular spaces were less prominent, the connective tissue much denser, the bone marrow cells almost totally absent. In these areas there was also formation of new bone trabeculæ.

Focal collections of myeloid cells were also found in the *kidneys* and the *pancreas*. The *cecum* showed two small ulcerations surrounded by lymphocytes, myeloid cells, and very few neutrophils. *Testes* were small and underdeveloped; the tubules were separated by a large amount of cellular connective tissue, and showed no spermatogenesis.

Case 2. L. S., white, male, age 67; No. 411030 (P. M. 10438). Except for a "nervous breakdown" a year before admission, the patient was always well. For the past 6 months he noted frequent appearance of "black and blue marks" without any obvious cause. This was accompanied by increasing fatigability and palpitation of the heart. A mild attack of cough about 2 weeks prior to admission was followed by persistent severe left-sided headache, repeated nosebleeds and marked weakness with night sweats. On admission, the temperature was 101° F., pulse 120. There were numerous purpuric spots over both elbows. The fundi showed flame-shaped and punctate hemorrhages. A sloughing ulcer and multiple bleeding points were found on the gums. The heart was enlarged, with apical and basal systolic murmur. The spleen reached 3 fingerbreadths and the liver 1 fingerbreadth below the costal arches. There was a pitting edema of both ankles. The subcutaneous lymph nodes were not

conspicuously enlarged. The blood count showed: Hgb. 34%, R.B.C. 1.3 mill., W.B.C. 8500 (31% segmented neutrophils and 2% non-segmented, 4% monocytes, 63% indetermined mononuclear cells and 2 normoblasts per 100 nucleated cells); platelets 80,000. A bone marrow biopsy showed replacement

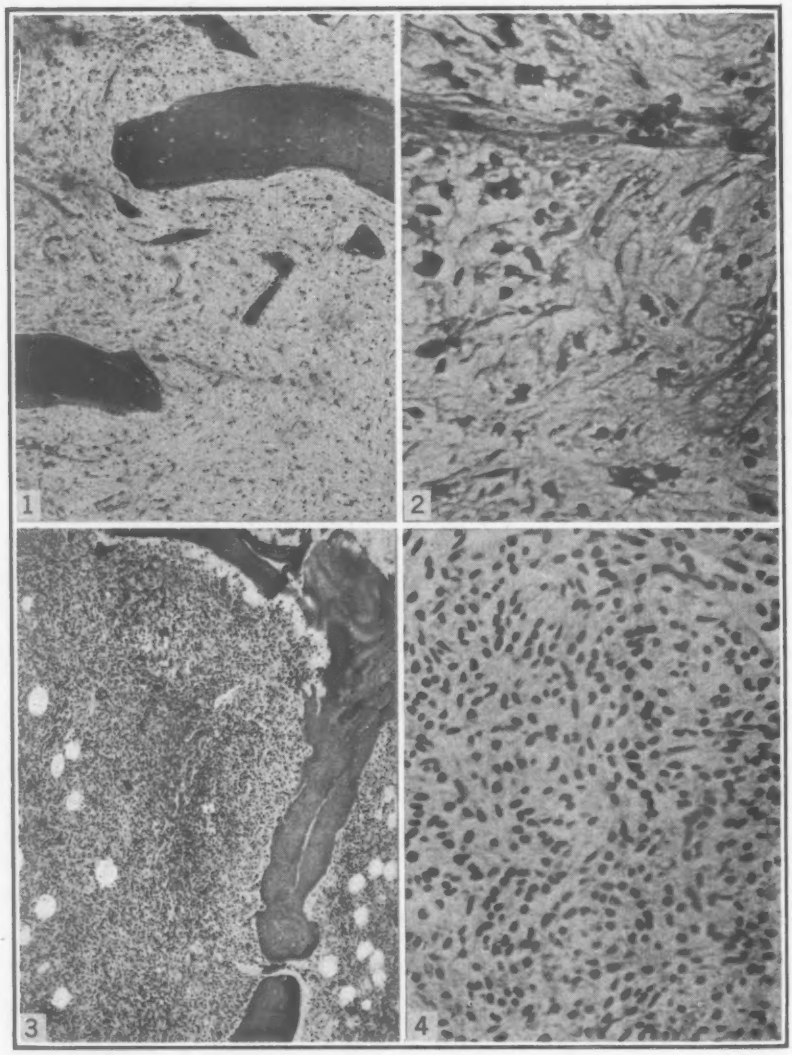

FIG. 1.—Case 1. *Bone marrow, subacute myeloid leukemia.* Replacement of the bone marrow by loose connective tissue and a few newly-formed bony trabeculæ. 75×.

FIG. 2.—Case 1. *Bone marrow.* Note the scattered myeloid cells. 360×.

FIG. 3.—Case 2. *Bone marrow, subacute myeloid leukemia.* Replacement of the normal marrow by cellular connective tissue and numerous myeloid cells. 75×.

FIG. 4.—Case 2. *Bone marrow.* 360×.

of the normal marrow by young connective tissue and young myeloid cells in a manner similar to that seen at autopsy. In spite of several large transfusions, the patient went rapidly downhill. His temperature rose to 104° F. in the next 4 days and remained at that level until his death, 9 days after admission.

Autopsy (2½ hours after death). There were scattered small petechial spots over the chest and over both arms and thighs. The gums appeared spongy and showed ulceration at the base of the lower incisors. Small petechial hemorrhages were found throughout the gastro-intestinal tract.

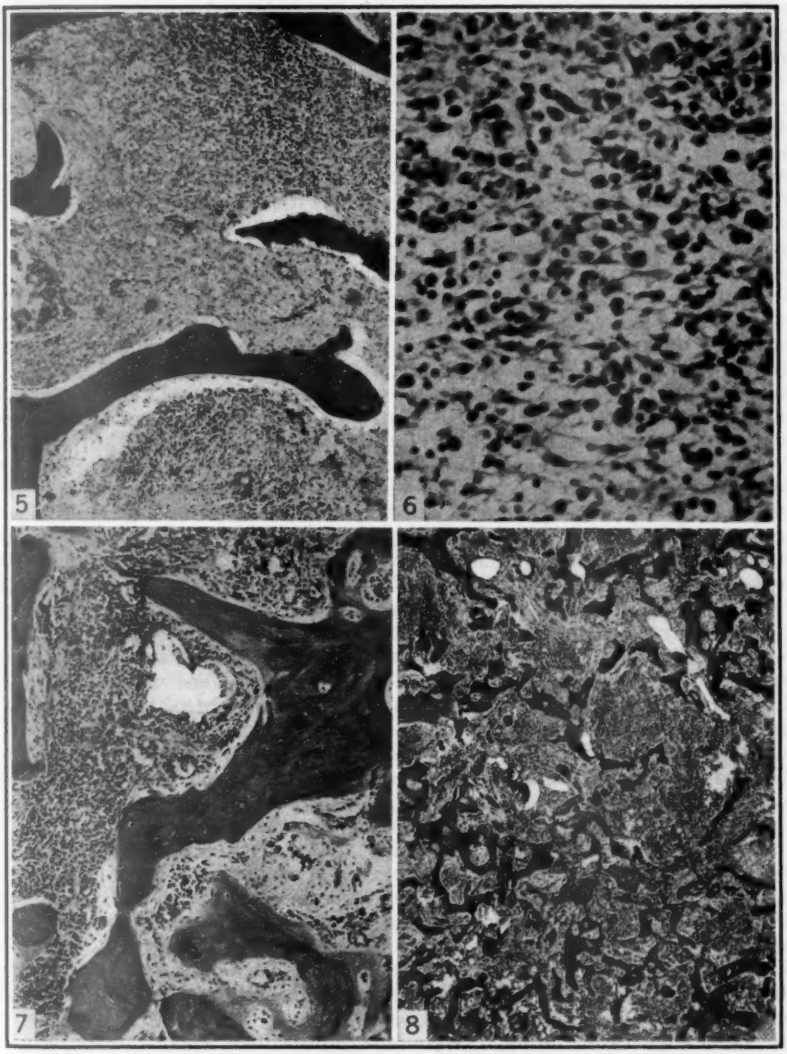

FIG. 5.—Case 3. *Bone marrow, chronic myeloid leukemia* treated with radiation. Fibrosis with islands of leukemic myeloid cells. 75×.

FIG. 6.—Case 3. *Bone marrow.* 360×.

FIG. 7.—Case 4. *Bone marrow, chronic non-leukemic myelosis.* Marked osteosclerosis and partial fibrosis. Note the enormous number of newly-formed bone trabeculæ and large areas of cellular marrow of normal composition. 95×.

FIG. 8.—Case 4. *Bone marrow.* 15×.

Heart: Enlarged, weighing 500 gm. The pericardial sac contained about 75 cc. of clear, serous fluid. There were a number of petechial hemorrhages in the parietal pericardium. A few petechiæ were also found under the endo-

cardium of the right and left auricle. The right ventricle was moderately, and the left ventricle markedly hypertrophied. All chambers of the heart were dilated. The myocardium of both ventricles was flabby, grayish brown in color, with areas of yellowish streaking.

Lungs: Over the posterior aspect of the right lung there was a continuous hemorrhagic area, 12 by 3 cm., extending for about 0.5 cm. into the parenchyma. Otherwise the lungs showed evidence of emphysema and, microscopically, focal infiltration of alveolar walls by young myeloid cells.

Liver (weight 2500 gm.) was enlarged and flabby. The cut section presented a distinct lobular architecture. The periportal fields were wide, brownish yellow and slightly elevated. The central zones were reddish brown and depressed. Under the microscope, the periportal fields were rather densely infiltrated, while the sinusoids contained only a few scattered abnormal cells. The infiltration consisted partly of large cells with large clear nuclei, partly of small cells with dark nuclei and scanty cytoplasm. Only a few maturing white elements were seen. There were no erythroblasts or megakaryocytes.

Spleen (weight 1800 gm.) was markedly enlarged and firm in consistency. The surface was purplish blue with irregular grayish white thickening of the capsule. The cut surface was light red in color, with irregular but well demarcated darker red areas, from pinhead to 2 cm. in diameter, scattered throughout the pulp. *Microscopically*, the spleen was densely infiltrated by cells similar to those found in the liver. Only a few of these cells gave a positive oxydase reaction. The Malpighian corpuscles could not be recognized. There were no foci of extramedullary blood formation.

Kidneys had a faintly granular surface. On microscopic examination they showed small scattered nests of myeloid cells.

Lymph Nodes: The abdominal and thoracic nodes were enlarged and measured up to 2 cm. in diameter. The cut surface was pinkish in color with irregular grayish areas. *Microscopically*, the normal architecture was preserved in places, but mostly obliterated by diffuse infiltration of myeloid cells. There were no erythroblasts or megakaryocytes

Bone Marrow: Sections through the lumbar vertebræ showed the usual bony trabeculation. The marrow was grayish red with scattered lighter yellowish areas. The sternal marrow was likewise grayish red and dry. Under the *microscope* (Figs. 3 and 4) the normal marrow had almost completely disappeared. The marrow spaces were filled with young myeloid cells, congested vascular channels and young connective tissue, in varying proportions. With the Mallory stain, the connective tissue fibers formed a dense network between and around the myeloid cells, and in places, aggregated into larger fibrous areas. A few islands of fatty marrow were also present.

Case 3. M. T., white, male, age 47, No. 482527 (P. M. 12048). The patient was in apparent good health until the end of November 1940, when the present illness began with fainting spells and passing of tarry stools. Gastric ulcer was suspected but not confirmed on Roentgen ray examination. At that time an enlarged spleen was noted in Roentgen ray films. Because of progressive loss of strength and weight the patient was hospitalized in March 1941. The physical examination revealed enlargement of the liver and spleen, the latter being the size of a grapefruit, and the former reaching 3 fingerbreadths below the costal arch. There were no palpable peripheral lymph nodes. Stool gave a positive test for occult blood. Repeated blood counts showed: Hgb. 80%, R.B.C. 4.7 to 4.85 mill., W.B.C. 79,600 to 132,000 (segmented neutrophils 37%, non-segmented 9%, metamyelocytes 9%, myelocytes 10%, promyelocytes 10%, myeloblasts 7%, eosinophils 3%, basophils 7%, lymphocytes 8%). Aspiration of sternal marrow was performed and showed: myeloblasts 11%, neutrophilic myelocytes 56.5%, eosinophilic 4%, basophilic 1.5%, neutrophils 27%; there was only 1 erythroblastic cell per 100 white cells. Diagnosis of myeloid leukemia was made and the patient was discharged after 1 Roentgen ray treatment to the left flank. In June 1941 a series of 6 Roentgen ray treatments to the spleen was administered in another institution (3 times a week, 100 rx3, anteriorly and posteriorly). The blood count before the treatment

was Hgb. 88%, R.B.C. 4.32 mill., W.B.C. 131,200 (myelocytes 4%, metamyelocytes 7%, neutrophils 70%, basophils 3%, monocytes 1%, lymphocytes 15%, nucleated red cells 4 per 100 W.B.C.). The white blood count dropped rapidly and at the conclusion of the irradiation series was below 10,000. Three weeks after the treatment the blood count was Hgb. 65%, R.B.C. 3.39 mill., W.B.C. 5000 (neutrophils 75%, monocytes 3%, lymphocytes 22%). The drop in the red blood cells and white blood cells persisted on all subsequent examinations.

At the time of admission (September, 1941), the liver reached 3 fingers and the spleen 6 fingers below the costal margin. There was no adenopathy. A flame-shaped hemorrhage was present in the fundus of the left eye. Blood count showed: Hgb. 64%, R.B.C. 3.36 mill., W.B.C. 1400 (myeloblasts 2%, myelocytes 10%, non-segmented 17%, segmented neutrophils 46%, basophils 1%, monocytes 2%, lymphocytes 25%, plasma cells 1%, normoblasts 1 per 100 W.B.C.; platelets 50,000; *Roentgen ray examination of the bones* revealed "several small osteoporotic areas in the distal end of the right femur, just above the condylar region, and in the proximal half inch of the right tibia. There is also a suggestion of osteoporosis of the descending ramus of the right pubic bone. The significance of these findings is not determined. In view of the clinical findings of leukemia, these are probably due to leukemic infiltrations. There is no periosteal elevation."

During his stay in the hospital, the patient developed a transient jaundice. Despite a temporary improvement after transfusions, the course was rapidly downhill. On his second admission in December 1941, the patient had fever and ascites. Both the liver and spleen were enormously enlarged, reaching down to the iliac crests. Blood count showed: Hgb. 58%, R.B.C. 3.2 mill., W.B.C. 7800 (myeloblasts 30%, neutrophilic myelocytes 3%, basophilic 1%, non-segmented neutrophils 12%, segmented 39%, monocytes 1%, lymphocytes 12%, plasma cells 2%); platelets 5000. The sternal marrow (aspiration) was predominantly myeloblastic as seen in leukemia. Patient became progressively more drowsy and died in pulmonary edema 13 months after the appearance of the first symptoms.

Autopsy (2 hours after death). *Liver:* Markedly enlarged (weight 2800 gm.). The consistency was softer than normal and the edge was rounded. Under the transparent capsule and throughout the liver on cut section, there were scattered numerous discrete and confluent, slightly depressed dark red areas, irregular in outline and varying in size from that of a pinhead to 2 cm. in diameter. These areas were more numerous in the left lobe and more prominent in the subcapsular region. The intervening liver parenchyma was yellowish brown with an occasional pin-point grayish area. The lobular structure was fairly distinct. On *microscopic examination* it could be seen that the dark red areas were caused by extensive focal hemorrhages with necrosis of liver cells. Otherwise the parenchyma appeared fairly normal except for a moderate degree of fatty infiltration. The sinusoids were dilated and contained myeloid cells, single and in small groups. Though the predominant cell was the myeloblast, myelocytes were also seen. There were many cells in mitosis. The Kupffer cells were prominent. The portal fields contained occasional small collections of lymphocytes, but were entirely free of leukemic cell infiltration. Nowhere were there any signs of extramedullary hemopoiesis.

Spleen weighed 880 gm. and was moderately firm. The surface was smooth and dark bluish purple. The cut surface presented a homogeneous fleshy reddish brown appearance; only the trabeculæ but not the follicles could be made out. A cherry-size accessory spleen of a similar structure was found near the hilus. *Microscopic examination:* The Malphigian corpuscles were very small. The section had a rather homogeneous appearance caused by a diffuse infiltration of the pulp by myeloid cells. The infiltration was moderately intense so that it did not obscure the vascular pattern of the red pulp. The sinusoids were clearly discernible; many of them contained small groups of myeloid cells. The amount of fibrous tissue was definitely increased throughout the spleen. Silver stain brought out the dense network of reticulum fibers mainly in the peritrabecular zones. Sections of the accessory spleen showed

less fibrosis but a more pronounced infiltration by myeloid cells. There were no foci of extramedullary blood formation in the spleen or in the accessory spleen.

Lymph Nodes: The periaortic, peripancreatic and portal lymph nodes were enlarged, grayish in color and soft in consistency. The cut surface appeared moist and cellular. *Microscopically*, all of the examined lymph nodes showed leukemic involvement of varying degree. In those most markedly involved, the normal architecture was considerably obliterated, though a few lymph follicles could still be seen beneath the capsule. The cortex between the follicles as well as the medulla were infiltrated by myeloid cells. The infiltration was diffuse, but not very dense, so that a considerable number of lymphocytes could still be seen between the myeloid cells. A number of giant cells with pink cytoplasm and multilobulated nuclei were scattered throughout the lymph nodes. Some of these cells bore a close resemblance to megakaryocytes. There were no erythroblastic elements. In other lymph nodes the leukemic infiltration was less intense and was limited mainly to the medulla, leaving the architecture practically undisturbed.

Bone Marrow: Because of the limited permission, examination was confined to the lumbar vertebræ. On section, the bony trabeculation appeared normal, while the marrow between the trabeculæ was grayish, rather firm and dry. On *microscopic examination* (Figs. 5 and 6) the bony trabeculæ were normal in width and number. The cellular as well as the fatty marrow were completely replaced by a network composed of fibroblasts and delicate fibers which assumed blue color with the Mallory collagen stain and black color after silver impregnation. The meshes of this network contained a fair number of leukemic myeloid elements together with occasional nests of erythroblastic cells and very few megakaryocytes.

All other organs showed no significant changes and no leukemic infiltrations. The lungs presented a healed primary tuberculous focus with calcified tracheal lymph nodes.

Case 4. M. D., white, female, age 60; No. 294186 (P. M. 6365). The patient was first seen at the Mount Sinai Hospital in 1914, when she underwent hysterectomy for uterine fibromyomata. At that time there was apparently no splenomegaly or hepatomegaly. In 1920, she was readmitted because of severe pain in the left upper quadrant, loss of appetite and weakness. The spleen and liver were markedly enlarged, the former descending down to the umbilicus and being tender to palpation, and the latter reaching 3 fingers below the costal arch. The inguinal lymph nodes were slightly enlarged but there was no generalized lymphadenopathy. Blood count showed: Hgb. 72%, R.B.C. 4.17 mill., W.B.C. 9800 (neutrophils 68%, eosinophils 0.5%, basophils 0.5%, myelocytes 13.5%, myeloblasts 5%, lymphocytes 10%, monocytes 2.5%, a few normoblasts in the smear); platelets 250,000. On that basis the diagnosis of leukemia was accepted as most likely.

After discharge from the hospital, the patient was observed in the hematology clinic until 1928. She was given Roentgen ray treatments, though with little success. Her liver and spleen continued to enlarge, the latter frequently being very tender. The general condition deteriorated, at first slowly and then rapidly. Hgb. and R.B.C. gradually dropped to 50% and 3.2 mill., respectively; W.B.C. varied between 8200 and 39,000 (50 to 60% neutrophils, 10 to 20% myelocytes and 8 to 11% myeloblasts). The platelet count always remained within the normal limits, around 200,000 to 250,000. Because of weakness and marked emaciation, she was again admitted to the hospital in August 1928. Despite transfusions, her anemia rapidly progressed. W.B.C. remained as previously, though on one occasion it rose to 125,000 (80.5% neutrophils, 10.5% myelocytes, 3% myeloblasts, 3.5% lymphocytes, 1% monocytes and 19 normoblasts per 100 W.B.C.). The patient developed pneumonia which, together with increasing cachexia, led to her death 3 weeks after admission. The total duration of her illness was over 8 years.

Autopsy (11 hours after death). *Heart:* Moderately enlarged. The coronary arteries were sclerotic. The myocardium showed scattered areas of fibrosis

and fatty changes in the muscle fibers. The capillaries were dilated and contained many myeloid cells, both young forms and polymorphonuclears. Under the epicardium there were small focal collections of similar cells.

Lungs: Both lower lobes contained diffuse areas of bronchopneumonia. These showed abundant fibrinous exudate and numerous polymorphonuclear leukocytes as well as young myeloid cells. Numerous giant cells with dark pleomorphic nuclei were found in all microscopic sections. Focal infiltrations by myeloid cells were seen in the peribronchial and perivascular areas.

Liver (weight 1800 gm). The right lobe was elongated and enlarged. The surface was smooth. On section the parenchyma presented a waxy reddish appearance with occasional grayish streaks. On *microscopic examination*, the sinusoids were dilated and filled with myeloid cells in all stages of development. There were also occasional giant cells, some of which resembled megakaryocytes. The Kupffer cells were very prominent. The liver cells, especially in the center of the lobules, contained fat droplets and hemosiderin. The periportal fields were free from infiltration. There were no erythroblastic elements.

Spleen: Markedly enlarged and weighed 660 gm. It was firm to touch. The surface was smooth and bluish gray in color with numerous scattered white areas of infarction. The splenic pulp was pinkish gray and did not scrape off easily. The Malpighian corpuscles were not visible. The microscope revealed a marked disturbance of the normal architecture. The Malpighian corpuscles had completely disappeared. The sinusoids of the red pulp were prominent but appeared to be widely separated by thickened Bilroth's cords. The latter showed a conspicuous increase in reticulum cells, fibroblasts and connective tissue fibers forming a fine network. The meshes of this network contained nests of myeloid cells in various stages of development, as well as small collections of erythroblastic cells. There was also a considerable number of megakaryocytes. The sinusoids were for the most part empty, though some of them contained red blood cells and small collections of myeloid cells. The endothelial lining of the sinusoids was very prominent.

Kidneys: The right kidney was larger than the left. The capsules stripped with great difficulty revealing irregular surfaces with several protruding small nodules. These were firm in consistency and grayish white in color. The pelvis of the right kidney contained numerous sand-like brownish calculi; similar calculi were found in the bladder. *Microscopically*, the grayish nodules are found to be small mesodermal tumors, composed of fibrous, fatty and myxomatous tissue. Scattered through the parenchyma of both kidneys were small foci of myeloid cells in various stages of development. A few giant cells of the megakaryocytic type were found in the capillaries and in the glomerular loops.

Gastro-intestinal Tract: The ileum and the colon presented several small superficial reddish gray areas of necrosis. The underlying submucosa and muscularis were infiltrated with neutrophils.

Lymph Nodes: The mesenteric and the retroperitoneal lymph nodes were moderately enlarged and rather firm in consistency. *Microscopically*, they showed a varying degree of myeloid metaplasia, with loss of normal structure. In some of the nodes the infiltration consisted almost exclusively of myeloid cells in various stages of development; in others, there were in addition prominent nests of erythroblasts and very numerous cells of the megakaryocytic type.

Bone Marrow: The tibia was opened for a short distance. Its marrow cavity was filled with spongy bone. Similarly, the marrow cavity of the lower third of the humerus was completely filled with spongy bone. The lumbar vertebræ had, on section, a dense spongy appearance and were pink in color. *Microscopic examination* (Figs. 7 and 8) showed a marked increase in the number of bony trabeculæ which were wide and tortuous and varied in their calcium content. There was also a striking formation of new bone and marked narrowing of marrow spaces. The latter were often frequently completely filled by fibrous tissue. Other areas of the bone marrow, in spite of the increase in connective tissue, were very cellular and contained numerous myeloid elements, erythroblastic cells and megakaryocytes in increased numbers.

Comment: The first 3 cases as can be seen from the descriptions (and the 3 not extensively reported here) are unequivocal examples of leukemia, according to the most generally accepted standards. They obviously fulfill the criteria as far as the clinical course, the blood picture and the pathologic findings are concerned.* The occurrence of foci of extramedullary blood formation in Case 1, and of giant cells in the lymph nodes in Case 3, is in accord with the leukemia concept.[16,17]

The fourth case presents a different picture. Clinically it was observed for 8 years and classified as chronic myeloid leukemia. The white blood count was elevated, reaching 125,000 on one occasion. Numerous immature white cells and nucleated red cells were regularly found in the circulating blood. The bones, including the long bones, exhibited osteosclerosis with areas of complete myelofibrosis, as well as areas of hyperplastic bone marrow. There were extensive infiltrations in the liver, spleen, lymph nodes and also small foci in pericardium and kidneys; the infiltrations consisted of myeloid cells in various stages of development, and of numerous megakaryocytes and erythroblasts, the latter being prominent in the lymph nodes and spleen. The same diversity without the customary preponderance of young white cells was observed in the hyperplastic foci of bone marrow. The long clinical course; the moderately elevated white blood cell count with a low proportion of primitive cells; the constant presence of nucleated red blood cells; the chronic splenomegaly; the absence of typical leukemic infiltrations, and the diversity of cells forming the infiltrations in the various organs with an unusually large number of megakaryocytes—all tend to place this case in the leukemoid[12] group of non-leukemic myelosis.

The changes in the bone marrow of the first 3 cases were of an essentially similar type. The available sections of bone (unfortunately no long bones could be examined because of the limited autopsy permissions) showed a varying degree of fibrosis. In Case 2 the marrow was cellular and characteristically leukemic; fibrosis was represented by a meshwork of fine threads of connective tissue; there was no appreciable change in the bony trabeculation. In Case 1, on the other hand, the bony trabeculation was somewhat denser than normal with occasional areas of newly formed bone. The hematic cells had all but completely disappeared from the marrow which was almost made entirely up of young mucoid, rather cellular connective tissue. Neither of these cases had received any Roentgen ray treatment. Case 3 presented similarly marked fibrosis, with still clearly discernible islands of leukemic myeloid cells, but without any definite increase in the bony trabeculation. This case belongs to the group of chronic myeloid leukemia and was treated with small doses of Roentgen ray, so that fibrosis can be attributed, at least in part, to the latter factor. However, it has to be pointed out that in our material only 4 out of 50

* The diagnostic criteria for the leukemias still are of a cumulative nature, rather than any one being pathognomonic. It is well recognized that a number of conditions can produce leukemoid[12] blood pictures as well as clinical signs and symptoms, and even the characteristic histologic picture can be simulated. One must be most careful, therefore, in the use of unreserved allocations.—EDITOR.

cases of chronic leukemia, showed fibrosis of the bone marrow though all of them received the standard treatment of this disease. To summarize, the osteodystrophic changes in the 6 cases of leukemia consisted of myelofibrosis—an increase in connective tissue within the marrow with replacement of the cellular elements. There was little or no formation of new bony trabeculæ and, therefore, the marrow spaces were not narrowed to any appreciable extent.

The appearance of the bone marrow in the fourth case, here reported —the non-leukemic myelosis—was dominated by a great amount of newly formed bone with marked narrowing of the marrow spaces. The latter were partly filled by connective tissue and partly by hyperplastic marrow. The trabeculæ were wide and tortuous and showed a varying degree of calcification. This is the typical picture of *osteosclerosis*, as defined by Kaufmann;[11] it is "the antithesis of osteoporosis and consists of the formation of new, at first osteoid, then calcified true bone, coming from the marrow and vessel cavities and encroaching upon the old trabeculæ. The spaces within the bone are filled with more and more bone tissue." Osteosclerosis is commonly accompanied by a varying degree of fibrosis of bone marrow, but, as demonstrated above, myelofibrosis occurs also without osteosclerosis.

The literature contains only a few examples of leukemia associated with myelofibrosis, though apparently it is not very rare. The case published by Lehndorff and Zak[13] is often called osteosclerotic leukemia, but in reality is a typical instance of myelofibrosis without a trace of osteosclerosis. Mettier and Rusk[15] reported 2 cases under the title: "Fibrosis of the bone marrow (myelofibrosis) associated with leukemoid blood picture." The case of Anagnostu[1] might also belong in this group.

Reports of "osteosclerotic leukemia" are more numerous. However, we agree with Carpenter and Flory[3] that the great majority of cases of osteosclerosis with a leukemic or leukemoid blood picture can be classified as non-leukemic myelosis. We were able to find only 2 cases which do not fulfill the criteria of non-leukemic myelosis and can be regarded as instances of leukemia, though by no means typical. The case of Jacobson[9] is reported very briefly and the details are lacking. It concerns a 28 year old chemist, who worked with pyridine and aniline dyes and developed a marked anemia and leukopenia with many atypical cells in the circulation. The postmortem examination revealed extensive osteosclerosis and typical leukemic infiltrations in the liver, spleen, kidneys and intestines. In the case of Haessler and Krauspe,[5] a girl aged 2 years and 8 months suffered from increasing anemia. The leukocytes varied between 2600 and 7200. No typical leukemic cells were found in the blood. The duration of the disease was 6 months. At autopsy there was marked generalized osteosclerosis with foci of typical leukemic bone marrow and extensive infiltration of many organs by leukemic cells with localized tumor formation. The existence of such cases points to the need of careful and unbiased examination in every instance of osteosclerosis associated with blood changes.

Summary and Conclusions. 1. Among 97 cases of leukemia, 6 showed a varying degree of myelofibrosis without osteosclerosis. Four of these cases were of the chronic myeloid type and were treated with Roentgen ray; the other 2 were diagnosed as subacute myeloid leukemia and did not receive any Roentgen ray therapy.

2. Myelofibrosis, not associated with osteosclerosis, is apparently not uncommon in the leukemias.

3. A case of osteosclerosis and leukemoid blood picture is described and interpreted as an instance of non-leukemic myelosis.

4. A review of the literature shows that osteosclerosis is often associated with non-leukemic myelosis and only very rarely, if at all, with true leukemia.

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DIAGNOSTIC PHYSICOCHEMICAL BLOOD TESTS IN SICKLE CELL ANEMIA

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In a recent study of the sedimentation rate in sickle cell anemia, it was noted that the sedimentation of the erythrocytes had certain characteristics which were not encountered in any other normal or disease states.[3] These features have a diagnostic value and may serve to supplement the other diagnostic procedures commonly employed.[1,2]

These characteristics may be organized and used as clinical diagnostic tests. Two separate tests are described, although they are based upon the same principles, *viz.*, the increase of the sedimentation rate of the erythrocyte of sickle anemia by O_2 and the reduction of the sedimentation rate by CO_2. The tests differ, therefore, only in the methods by which these changes are brought about. These tests are described since they emphasize certain physicochemical peculiarities of the blood in sickle cell anemia, and offer themselves as objective procedures for the diagnostic study of sickle cell anemia. They have certain definite advantages. First, they do not depend solely upon the sickling phenomenon for the diagnosis of sickle cell anemia. Second, they are rapidly performed, the total time frequently being appreciably less than the time required to perform the routine sedimentation rate. Third, they require only simple laboratory equipment. Fourth, they offer themselves as additional objective tests for use in the study of doubtful cases.

Methods. These studies are based on observations made on 26 patients with sickle cell anemia and 60 who were normal subjects or had other diseases. The diseased states included luetic hepatitis, peptic ulcer, aplastic anemia, essential, benign and malignant hypertension, pernicious anemia, malnutrition, amebiasis, carcinoma of the stomach, carcinoma of the esophagus, carcinoma of the rectum, pregnancy, acute and chronic gastritis, luetic heart disease, gout, ulcerative colitis, pulmonary tuberculosis, pyelitis, tuberculous peritonitis, disseminated lupus erythematosis, pneumococcus and virus pneumonia, Weil's disease, myelogenous leukemia and acromegaly. A total of 371 determinations were made on the blood of patients with sickle cell anemia and 239 determinations on the control patients. These observations indicated the characteristic effects of O_2 and CO_2 upon the sedimentation rate of the erythrocytes of sickle cell anemia and led to the formulation of two diagnostic procedures which were studied in detail in 14 patients with sickle cell anemia and 20 with other disorders. The two suggested diagnostic procedures are as follows:

1. *Oxygen-Carbon Dioxide Technique.* A tourniquet is placed on the arm and blood is removed. The entire operation should not take more than 60 seconds. This is important to keep the collection standard. Approximately 9½ cc. of venous blood are placed in a 10 cc. vial containing 6 mg. of dry ammonium oxylate and 4 mg. of dry potassium oxylate. Five cc. is sufficient, however. In these studies the larger volume was used in order that duplicates could be made. The vial is immediately corked, and rotated for not longer than 3 minutes. Half of the blood is poured into a flask containing oxygen and half into one containing carbon dioxide.* These are rotated intermittently for 15 minutes after which sedimentation rates are determined for each blood sample according to the method described by Wintrobe.[4]

2. *Aëration-Tourniquet Technique.* Venous blood is removed under standard conditions as described above. Five cc. of blood is placed in a small beaker or Erlenmeyer flask and is rotated in air for 15 minutes after which a sedimentation rate is determined. A sphygmomanometer cuff inflated to a pressure just above the diastolic is allowed to remain on the arm for 6 minutes after which blood is drawn and a second sedimentation rate is determined.

It has been found (these studies and previous ones[2]) that the method functions as well and may be simplified if the tourniquet (inflated blood pressure

* Oxygen and carbon dioxide had previously been run into 2 separate 50-cc. Erlenmeyer flasks. These were corked with rubber stoppers and were stored until ready for use. The amount of gas lost while pipeting the blood from the vial to the flask did not alter the results, as 100% gas is not necessary for the test (*vida infra*).

cuff) is applied for 6 minutes and 5 cc. of blood is collected as described above. A sedimentation rate is then determined immediately on the blood; the remainder is rotated for 15 minutes in air in a small Erlenmeyer flask and then a sedimentation rate is determined on the aërated blood. This procedure offers a definite advantage in that a venepuncture is performed only once.

Results. The results of the oxygen-carbon dioxide test are summarized in Table 1. It may be seen that in patients with sickle cell anemia, oxygen accelerates and carbon dioxide retards the sedimentation rate compared with that of venous blood run immediately upon removal from the patient. There was a mean acceleration by O_2 of 28.3 mm. of the initial sedimentation rate of venous blood (the rate being doubled) and a mean deceleration by CO_2 of 23.3 mm. (the rate being reduced more than 20 times).

TABLE 1.—THE EFFECT OF O_2 AND CO_2 ON THE SEDIMENTATION RATE OF 8 PATIENTS WITH SICKLE CELL ANEMIA AND 14 PATIENTS WITH OTHER CONDITIONS

(The "diagnostic parameters" [Δ_1] are listed in the last column)

Subject No., or diagnosis	No. of individual determinations	Average sedimentation rate (Wintrobe) (mm./hr.)			Acceleration of SR. (SR. in O_2) minus (SR. in venous blood) (mm./hr.)	Retardation of SR. (SR. in venous blood) minus (SR. in CO_2) (mm./hr.)	Diagnostic parameter (SR. in O_2) minus (SR. in CO_2) (mm./hr.)
		Venous blood	O_2	CO_2			
Sickle Cell Anemia Patients							
1	4	36.0	40.0	0.0	4.0	36.0	40.0
2	1	35.0	70.0	0.0	35.0	35.0	70.0
3	2	14.0	62.0	1.0	48.0	13.0	61.0
4	1	7.0	67.0	3.0	60.0	4.0	64.0
5	2	31.0	51.0	1.0	20.0	30.0	50.0
6	2	11.0	40.0	1.0	29.0	10.0	39.0
7	3	26.0	52.0	2.0	26.0	24.0	50.0
8	1	36.0	41.0	1.0	5.0	35.0	40.0
Mean	...	24.5	52.8	1.1	28.3	23.3	51.7
Maximum	...	36.0	70.0	3.0	60.0	36.0	70.0
Minimum	...	7.0	40.0	0.0	4.0	4.0	39.0
Control Patients							
Pernicious anemia	4	70.0	66.0	60.0	−4.0	10.0	6.0
Peptic ulcer	1	16.0	20.0	13.0	4.0	3.0	7.0
Peptic ulcer	1	60.0	59.0	56.0	−1.0	4.0	3.0
Peptic ulcer	1	66.0	65.0	63.0	−1.0	3.0	2.0
Amebiasis	1	48.0	46.0	40.0	−2.0	8.0	6.0
Ca. stomach	1	50.0	50.0	41.0	0.0	9.0	9.0
Malnutrition	1	50.0	48.0	31.0	−2.0	19.0	17.0
Pernicious anemia	1	35.0	39.0	20.0	4.0	15.0	19.0
Pregnancy	1	60.0	61.0	60.0	1.0	0.0	1.0
Malnutrition	1	34.0	31.0	23.0	−3.0	11.0	8.0
Ca. rectum	1	15.0	20.0	15.0	5.0	0.0	5.0
Gastritis	1	32.0	38.0	24.0	6.0	8.0	14.0
Cardiac disease	1	55.0	55.0	47.0	0.0	8.0	8.0
Normal patient	1	6.0	5.0	4.0	−1.0	2.0	1.0
Mean	...	42.6	43.1	35.5	0.4	7.1	7.5
Maximum	...	70.0	66.0	63.0	6.0	19.0	19.0
Minimum	...	6.0	5.0	4.0	−4.0	0.0	1.0

The relative effect of saturating the blood of patients with sickle cell anemia with oxygen, or carbon dioxide, on the sedimentation rate, depends on the initial sedimentation rate of the venous blood. If the initial sedimentation rate of venous blood is slow, the oxygen will pro-

duce a marked acceleration of rate, whereas the carbon dioxide will produce a slight retardation. Conversely, when the initial sedimentation rate of venous blood is rapid, the acceleration of the rate by oxygen is slight and the retardation by carbon dioxide is marked.

The results of the aëration-tourniquet test are summarized in Table 2. In patients with sickle cell anemia, aëration of venous blood accelerates and the application of a tourniquet retards the sedimentation rates when compared with the sedimentation rate of unaltered venous blood.

TABLE 2.—THE EFFECT OF AËRATION OF BLOOD AND THE APPLICATION OF A TOURNIQUET ON THE SEDIMENTATION RATE IN 6 PATIENTS WITH SICKLE CELL ANEMIA

(The "diagnostic parameter" [Δ_3] has been calculated as indicated in the heading of the last column)

Subject No. or diagnosis	No. of individual determinations	Average sedimentation rate (Wintrobe) (mm./ hr.)			Acceleration of SR. (SR. after aëration) minus (SR. in venous blood) (mm./hr.)	Retardation of SR. (SR. in venous blood) minus (SR. after tourniquet) (mm./hr.)	Diagnostic parameter (SR. after aëration) minus (SR. after tourniquet) (mm./hr.)
		Venous blood	After aëration	After tourniquet			
Sickle Cell Anemia Patients							
1	1	7.0	69.0	3.0	62.0	4.0	66.0
2	2	6.0	39.0	2.0	33.0	4.0	37.0
3	1	1.0	66.0	1.0	65.0	0.0	65.0
4	1	7.0	39.0	1.0	32.0	6.0	38.0
5	1	31.0	68.0	3.0	37.0	28.0	65.0
6	2	36.0	40.0	3.0	4.0	33.0	37.0
Mean	..	14.6	53.5	2.1	38.8	12.5	51.3
Maximum	..	36.0	69.0	3.0	65.0	33.0	66.0
Minimum	..	1.0	39.0	1.0	4.0	0.0	37.0
Control Patients							
Luetic hepatitis	1	16.0	16.0	11.0	0.0	5.0	5.0
Peptic ulcer	1	47.0	46.0	49.0	−1.0	−2.0	−3.0
Aplastic anemia	1	50.0	50.0	48.0	0.0	2.0	2.0
Essential hypertension	1	49.0	48.0	47.0	−1.0	2.0	1.0
Pernicious anemia	1	30.0	30.0	26.0	0.0	4.0	4.0
Malnutrition	1	26.0	25.0	20.0	−1.0	6.0	5.0
Mean	..	36.3	35.8	33.5	−0 5	2.8	2.3
Maximum	..	49.0	50.0	47.0	0.0	6.0	5.0
Minimum	..	16.0	16.0	11.0	−1.0	−2.0	−3.0

Aëration of venous blood produced a mean increase in the sedimentation rate of 38.8 mm. over that for venous blood (an increase of about 2.5 times), while venous stasis produced by a tourniquet resulted in a mean decrease in the sedimentation rate of 12.5 mm. (a decrease of 6 times). Here, as in the oxygen-carbon dioxide method, the degree of acceleration, or retardation depends upon the initial sedimentation rate of venous blood. It is to be noted that the average acceleration of the sedimentation rate due to aëration is greater than the retardation due to the application of the tourniquet (Table 4).

The effects produced by the two procedures, upon the sedimentation rates of the erythrocytes of sickle cell anemia is considerably greater than that for the control subjects (Tables 1 and 2).

The Diagnostic Parameter. In order to utilize the lability of the sedimentation rate so that it might aid in the diagnosis of sickle cell

TABLE 3.—STATISTICAL ANALYSIS OF DATA PRESENTED IN TABLE 1

	(SR. in O_2) minus (SR. in venous blood) (mm./hr.)	(SR. in venous blood minus (SR. in CO_2) (mm./hr.)	Diagnostic parameter (SR. in O_2) minus (SR. in CO_2) (mm./hr.)
Sickle Cell Anemia Patients			
Mean	28.3	23.3	51.7
Estimated standard deviation	±19.4	±12.7	±12.0
Standard error of mean	±6.8	±4.5	±4.2
Mean / Standard error of mean	4.1	5.2	12.2
Probability	<0.01	<0.01	<0.01
Control Patients			
Mean	0.4	7.1	7.5
Estimated standard deviation	±3.1	±5.6	±5.6
Standard error of mean	±0.8	±1.5	±1.5
Mean / Standard error of mean	0.5	4.8	5.0
Probability	>0.6	<0.01	<0.01
Comparison of Means			
Difference	27.9	16.2	44.2
Standard error of difference	±5.2	±3.9	±3.8
Difference / Standard error of difference	5.4	4.2	11.6
Probability	<0.01	<0.01	<0.01

TABLE 4.—STATISTICAL ANALYSIS OF DATA PRESENTED IN TABLE 2

	(SR. after aëration) minus (SR. in venous blood) (mm./hr.)	(SR. in venous blood) minus (SR. after tourniquet) (mm./hr.)	Diagnostic parameter (SR. after aëration) minus (SR. after tourniquet) (mm./hr.)
Sickle Cell Anemia Patients			
Mean	38.8	12.5	51.3
Estimated standard deviation	±22.4	±14.2	±15.3
Standard error of mean	±9.2	±5.8	±6.2
Mean / Standard error of mean	4.2	2.2	8.2
Probability	<0.01	>0.05	<0.01
Control Patients			
Mean	−0.5	2.8	2.3
Estimated standard deviation	±0.5	±2.8	±3.07
Standard error of mean	±0.2	±1.2	±1.2
Mean / Standard error of mean	2.2	2.4	1.8
Probability	>0.05	>0.05	>0.01
Comparison of Means			
Difference	39.3	9.7	49.0
Standard error of difference	±9.2	±5.9	±6.4
Difference / Standard error of difference	4.3	1.6	7.7
Probability	<0.01	>0.1	<0.01

anemia, the degree of acceleration and retardation by O_2 and CO_2 respectively, must be considered in relation to each other. In order to do this, a "diagnostic parameter" is calculated (Tables 1 and 2), as described below.

1. When the oxygen-carbon dioxide technique is used, the diagnostic parameter (Δ_1) may be stated as the difference between the sedimentation rate in oxygen and the sedimentation rate in carbon dioxide: $\Delta_1 = \psi_1$. ψ_1 is equal to the sedimentation rate in O_2 minus the sedimentation rate in CO_2. If Δ_1 is greater than 27 mm. per hour, the test is "positive" and it is probable (98 chances out of 100) that the patient has active sickle cell anemia (Fig. 1). The value 27 was determined statistically (see Appendix).

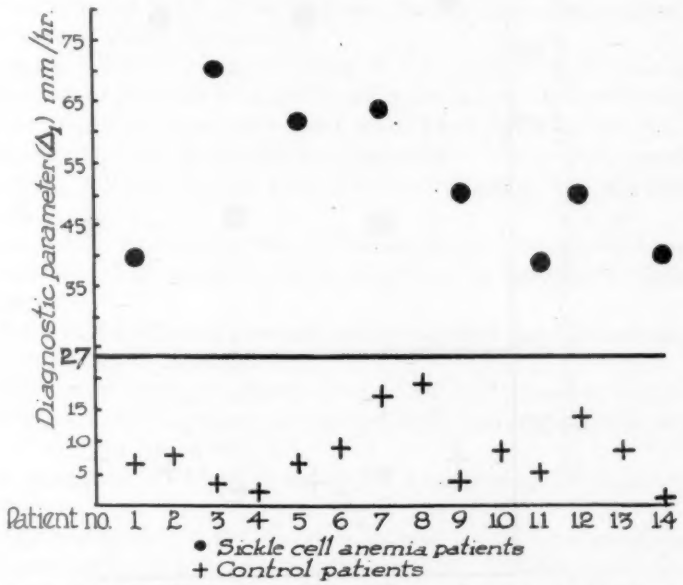

FIG. 1.—The diagnostic parameters (Δ_1) obtained by means of the oxygen-carbon dioxide technique in 8 patients with sickle cell anemia and 14 patients with other conditions. The values are shown in relation to the parameter of 27 mm./hr., a value found statistically, which separates patients with sickle cell anemia from those with other clinical states.

2. When the aëration-tourniquet technique is used, the diagnostic parameter (Δ_2) may be stated as the difference between the sedimentation rate of the aërated blood and the sedimentation of the non-aërated blood after the application of a tourniquet: $\Delta_2 = \psi_2$. ψ_2 is equal to the sedimentation rate after aëration minus the sedimentation rate of non-aërated blood after applying the tourniquet. If the Δ_2 is greater than 20 mm. per hour, the test is "positive" and it is probable (98 chances out of 100) that the patient has active sickle cell anemia (Fig. 2). The value 20 was determined statistically (see Appendix).

Discussion. The erythrocytes of patients with sickle cell anemia are peculiar in their response to saturation with O_2 and CO_2. The for-

mer produces a marked acceleration of the sedimentation rate, while the latter produces a marked retardation. These effects may be found to a slight degree in patients with other clinical states, but not nearly to the extent seen in sickle cell anemia. The consistency and the range of these changes immediately suggested their diagnostic, as well as their physicochemical importance. In fact, when the acceleration and retardation of the sedimentation rate by these two gases are expressed as functions of each other in order to arrive at a value that might have diagnostic significance and at the same time control the variability of the sedimentation rate as found in venous blood, a significant expression was obtained. This expression was arbitrarily

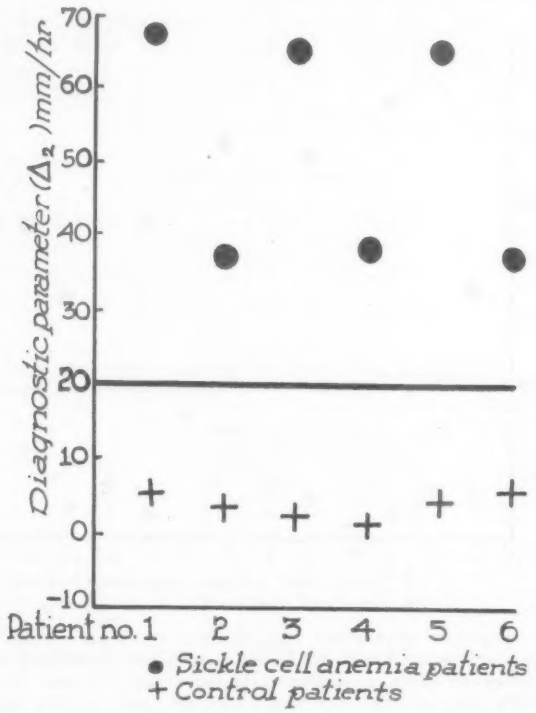

FIG. 2.—The diagnostic parameters (Δ_2) obtained by means of the aëration-tourniquet technique in 6 patients with sickle cell anemia and 6 patients with other conditions. The values are shown in relation to the parameter of 20 mm./hr., a value found statistically, which separates patients with sickle cell anemia from those with other clinical states.

called the "diagnostic parameter." When these data were tested statistically, it was found to have a 98% accuracy in the diagnosis of sickle cell anemia. The control subjects had 4 chances in much more than 10,000 of falling within the range for sickle cell anemia blood when the oxygen-carbon dioxide test is used, and 1 chance in much more than 10,000 of falling within the range of sickle cell anemia blood when the aëration-tourniquet test is used (see Appendix for statistical data).

The aëration-tourniquet test is the more simple of the two procedures

since it does not require that pure O_2 and CO_2 be available. All that is needed are sedimentation tubes, a clinical blood pressure apparatus and syringe and needle. Furthermore, this method can be simplified so that only 1 venepuncture is necessary (see Method).

It is not suggested that these tests be used to replace the microscopic study of the erythrocyte for the sickling phenomenon. They are to be used when one is in need of quick diagnosis, as would be encountered when the abdominal crises are confused with acute surgical conditions in the abdomen. It is not the purpose of this discussion to point out the dangers of surgical procedures in these patients.

It has been found in most instances, that after the blood has been placed in the sedimentation tubes, the diagnostic parameter is reached within 15 to 20 minutes. It is not necessary to carry the test out to a full hour under those circumstances, thus reducing the entire time for the test to about 30 minutes.

Summary. The marked retarding of the sedimentation rate of the erythrocytes of patients with sickle cell anemia by CO_2 and the marked acceleration by oxygen were used as a basis for two simple rapid macroscopic tests for active sickle cell anemia. These tests were found to be 98% reliable in the identification of sickle cell anemia (see Appendix).

The aëration tourniquet test is the simpler to perform and requires less material. The method can be simplified to involve the following procedures:

1. A tourniquet (blood pressure cuff) is applied to an arm to produce venous stasis for 6 minutes.
2. Five cc. of blood are drawn from a vein and placed in a small vial containing an anticoagulant, stoppered and rotated gently in order to avoid mixing the blood with air.
3. A sample of the blood is set up for a sedimentation measurement immediately.
4. The remainder of the blood is rotated in air in a small beaker, or Erlenmeyer flask, to saturate it thoroughly. A sedimentation rate is then determined on this aërated blood.
5. Within 15 to 60 minutes the diagnostic parameter (Δ_2) should be greater than 20 mm. per hour if the patient has sickle cell anemia. As soon as this parameter is reached, it is not necessary to continue the sedimentation rate to a full hour.

Conclusion. The aëration-tourniquet test not only is simple and rapid, but it serves as a check on the microscopic study of sickling which is often not properly done, or is late in showing evidence of sickling—often too late for the proper management of diagnostic problems of acute abdominal conditions which may, or may not, require surgical intervention.

APPENDIX

Statistical Analysis

Oxygen-Carbon Dioxide Technique. The diagnostic parameter (Δ_1) shown in Table 1 is the difference between the sedimentation rate in O_2 and the sedi-

mentation rate in CO_2 and thus is independent of the sedimentation rate in venous blood. The mean values (Table 3) for Δ_1 for both the sickle cell anemia patients and the control patients are statistically reliable. The probability of less than 0.01 ($P < 0.01$) means that in less than 1% of such samples of sickle cell anemia patients and control patients are mean values, as great or greater than those shown in Table 1, likely to be obtained by chance alone.

The difference between the mean values of the diagnostic parameter for these two groups of patients is sufficient statistical evidence that there are factors present in the sickle cell anemia patients producing a high diagnostic parameter which are evidently absent in the control patients.

Aëration-Tourniquet Technique. The diagnostic parameter (Δ_2) shown in Table 2 is the difference between the sedimentation rate after aëration and the sedimentation rate after application of the tourniquet. The mean value shown in Table 4 (Δ_2) for the sickle cell anemia patients on whom this technique was used is statistically reliable, the probability being determined as $P < 0.01$. The mean value of the diagnostic parameter for the control patients in whom this technique was used is not statistically reliable, because there is no statistical evidence of consistent alteration of the sedimentation rate produced by either the application of the tourniquet, or the aëration of the blood.

The analysis stated above for the difference between the mean values of the diagnostic parameter for the two groups of patients on whom the CO_2-O_2 technique was used also applied when using the tourniquet-aëration method.

Lower Limit of the Diagnostic Parameter. A value of 27 mm./hr. is established as the lower limit of the diagnostic parameter (Δ_1) accepted for the diagnosis of sickle cell anemia using the O_2-CO_2 technique. This value equals the computed mean of Δ_1 for the sickle cell anemia patients minus 2.05 estimated standard deviations ($M - 2.05\ \sigma$). Approximately 98% (97.98%) of sickle cell anemia patients may be expected to have a diagnostic parameter equal to or greater than this value. Assuming that the diagnostic parameter obtained for the control patients represents those values that would be obtained for patients with other types of anemia and infections, the probability that any such patient would have a diagnostic parameter greater than 27 mm. hr. is determined as $P < 0.0004$. Thus less than 4 of 10,000 patients are likely to be incorrectly diagnosed as having sickle cell anemia.

A value of 20 mm./hr. was established as the lower limit of the diagnostic parameter (Δ_2) accepted for the diagnosis of sickle cell anemia using the aëration-tourniquet technique. This value equals the computed mean of Δ_2 for the sickle cell anemia patients minus 2.04 estimated standard deviations ($M - 2.04\ \sigma$). Approximately 98% (97.93%) of sickle cell anemia patients may be expected to have a diagnostic parameter equal to or greater than this value. Again assuming that the diagnostic parameter obtained for the control patients represents those values that would be obtained for patients with other types of anemia and infections, the probability that any such patient would have a diagnostic parameter greater than 20 mm./hr. is determined as $P < 0.0001$. Thus less than 1 of 10,000 patients on whom the aëration-tourniquet technique is used are likely to be incorrectly diagnosed as having sickle cell anemia.

We wish to express our appreciation to Mr. R. J. Hammerstrom, of the Department of Preventive Medicine, for his valuable help in these statistical studies.

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HAND–SCHÜLLER–CHRISTIAN'S SYNDROME AND "EOSINOPHILIC OR SOLITARY GRANULOMA OF BONE"

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Snapper,[7] in a chapter devoted to Schüller-Christian's disease refers to patients suffering from lipoidal granulomas of the long bones with absence of granulomas of the cranium. He also mentions the hypothesis that the proliferation of the reticulo-endothelial system with granuloma formation is a primary phenomenon of these xanthomatoses, and insists particularly on the importance of choosing the lesion from which the biopsy is to be made in order to avoid mistakes in diagnosis.

The publications of Otani and Ehrlich,[6] Lichtenstein and Jaffe,[5] Bass,[1] Farber,[2] Green, and Farber[3] and Gross and Jacox[4] produced more extensive discussion of this subject; clinicians and pathologists are still attempting to clear up divergencies as to the nature of Hand-Christian's disease and of eosinophilic or solitary granuloma of the bones, isolated xanthomas and the non-lipoid reticulo-endotheliosis of Letterer-Siwe.

We consequently, in this paper, offer this contribution towards elucidating the question.

Report of a Case. The patient, M. Q. (Fig. 1), Spanish, 50 years old, resident in Brazil since she was 40 days old, married at 16, and has had 15 pregnancies, of which 12 children are alive and physically well developed; 1 child died suddenly when it was 27 days old, cause unknown. The first and last pregnancies ended in abortion at 4 months. After the last abortion, in the middle of 1940, there followed a period of menorrhagia which lasted 8 months and was cured by uterine curettage. She has suffered from measles but there is no history of traumatism.

While suffering from menorrhagia she began to feel, in the central region of the left thigh, stabbing pains followed by short periods of relief. The Roentgen ray examination made in Rio de Janeiro in April, 1941, showed a fusiform area of rarefied bone in the middle of the diaphysis of the left femur (Fig. 2). The Wassermann and Kahn tests were negative, but Müller's test was slightly positive, but negative on August 9, 1941, after antisyphilitic treatment. The patient's painful symptoms were relieved and she returned to her home in Minas. The teeth, which by then were loose, began to fall out and shortly afterwards the pain the left thigh reappeared, now however, radiating to the hip and knee on the same side. On May 20, 1942, while hurrying to catch a train, she suffered a fracture of the left thigh (Fig. 3) and was admitted to First-Aid Hospital.

FIG. 1.—Patient M. Q.; no exophthalmia can be seen.

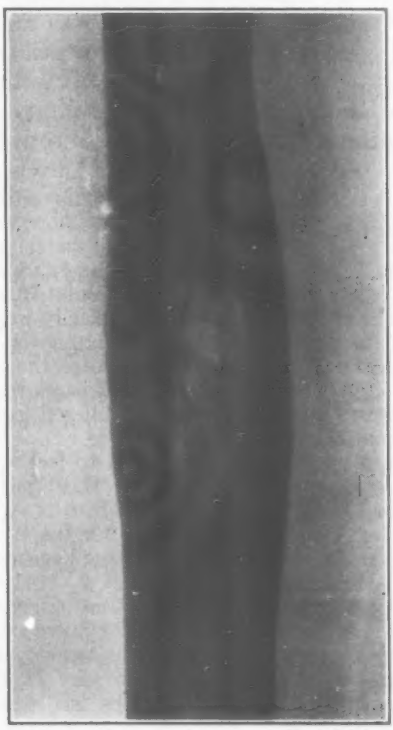

FIG. 2.—Radiograph of the middle part of the diaphysis of the left femur showing the shadow of the rarefied lacuna in April, 1941.

Physical Examination. The patient was badly nourished. Many teeth were lost, the few remaining being secured only by the soft tissues. There was pyorrhea and polydipsia; no exophthalmia; the sclera slightly bluish; the fundi normal. There was a pathologic fracture at the junction of the middle and upper third of the left femur occurring near an oval lacuna shadow of irregular outline measuring about 6 cm. long. Below this there were 2 other smaller shadows of identical aspect. The compact bone tissue was attacked (Fig. 3). The liver and spleen were normal.

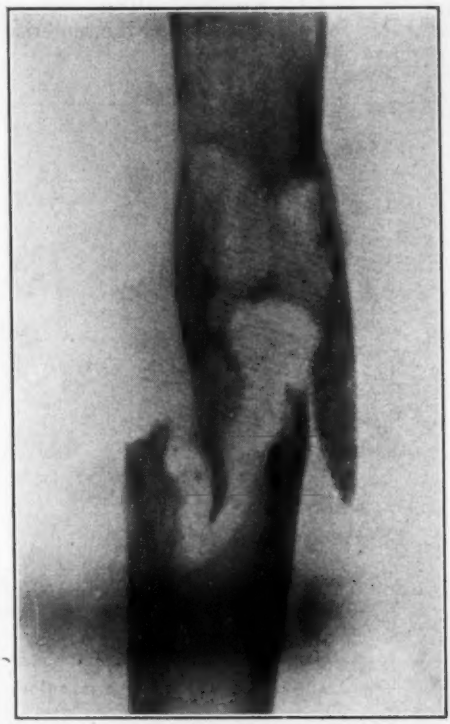

FIG. 3.—Radiograph of the middle part of the diaphysis of the left femur showing fracture at the set of osseous rarefaction in May, 1942.

Laboratory Examinations. Urine: volume in 24 hours, 5780 cc.; density at 150, 1006; no albumin, glucose or other abnormal substances (including Bence-Jones' protein). Blood: hemoglobin, 9.92 gm. (Sahli); erythrocytes, 4,065,000; leukocytes, 8400 (neutrophils, 48%; eosinophils, 6.5%; mast cells, 1%; lymphocytes, 40%; monocytes, 4.5%). Glucose, 74 mg. per 100 cc.; uric acid, 2.48 mg. per 100 cc.; cholesterol, 134; inorganic phosphates, 2.8; calcium, 13.5; phosphatase (Kay), 0.08 unit. In the feces there were eggs of *A. lumbricoides* and *T. trichiura.*

Myelogram (sternal puncture): Hemohistoblasts with neutrophil granules, 0.4%; proneutrophil myeloblasts, 0.4%; neutrophil promyelocytes, 2.6%; neutrophil myelocytes, 13.6%; neutrophil metamyelocytes, 8.2% polymorphonuclear neutrophils, 36%; eosinophil myelocytes, 2.2%; eosinophil metamyelocytes, 1.8%; polymorphonuclear eosinophils, 3.2%; lymphocytes, 10.4%; mast cells, 0.2%; monocytes, 0.2%; megaloblasts, 0.4%; megaloblasts in mitosis, 0.2%; proerythroblasts, 0.4%; basophil erythroblasts, 1.4%; polychromatophil erythroblasts, 0.6%; orthochromatic erythroblasts, 15%; megacaryocytes, 0.2%; plasma cells, 2.4%; Türck cells, 0.2%.

Roentgen ray films of skull bones, pelvis, right femur, tibia, humerus, ribs, maxillary bones and lungs showed nothing of interest.

Diagnosis. Intestinal worms. Pathologic fracture of the left femur. Hand-Christian's syndrome.

The curetting of the focus of fracture, as the first stage towards irradiation or bone grafting, was done by one of us (J. M. F.) on May 5, and showed the existence of a yellowish, spongy-looking tissue projecting from the fractured part and extending along the medullary zone of the femur; samples of this were taken for histopathologic examination.

Pathologic Report (M. A. J.). No. 3857. Ten small samples, previously fixed in alcohol, were sent for examination; all the material was embedded in paraffin.

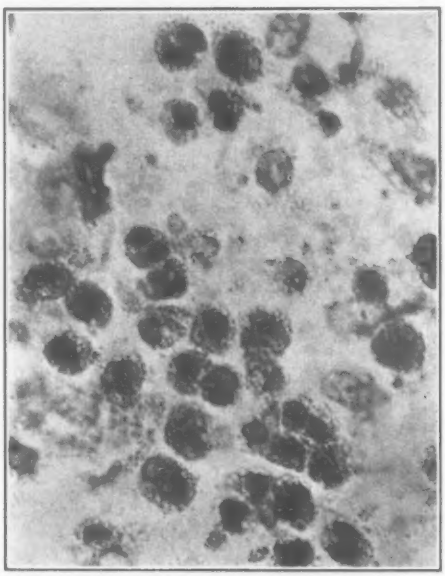

FIG. 4.—Eosinophilic infiltration of the granuloma.

The sections showed that large areas of these fragments had undergone necrosis with hemorrhage, and around these areas could be seen rounded cells with abundant protoplasm enclosing, phagocytic fashion, a greenish-yellow pigment (a hematic pigment giving the Berlin blue reaction). Among these cells there were some multinuclear ones which at times also contained pigment. In the peripheral zone of some samples, the reticulo-endothelial structure could be identified with thickening of the reticulum and cellular hyperplasia, here also were some multinuclear cells, looking like Reed-Sternberg cells.

Some areas were infiltrated by eosinophils which, in some places, were so compact that they produced the appearance of a true eosinophil granuloma (Fig. 4).

One sample looked like xanthomatous tissue, consisting of bulky cells with central nucleus and foam-like protoplasm; some multinuclear giant cells (Touton cells) were also seen (Figs. 5 and 6). All these cells lay amidst a thickened reticulum, and in a limited peripheral area, some mast cells could be seen. In this sample only 2 small trabeculæ were seen, one of them with signs of decalcification.

Treatment and Evolution. The treatment prescribed by us was vitamins A and D and extract of the posterior lobe of the hypophysis. The latter was at first administered through the skin (Retrophysina) and later through the nose (retrohypophysis powder—Slopart's snuff). There was no marked altera-

tion of blood pressure. The polydipsia disappeared and the flow of urine became normal; but both these conditions have, up to the present, reappeared when the hypophysis extract medication is discontinued. As a proof of this it is sufficient to state that on January 11, 1943, after a 3 day interruption of the hypophysis medication, the volume of urine increased to 12 liters in 24 hours, and the calciuria was 380 mg. (expressed as calcium—Shohl and Pedley's method). On the same date the serum's calcium content was 12.5 mg. per 100 cc., the phosphates 4.8 mg. per 100 cc. and the phosphatase 0.19 unit (Kay).

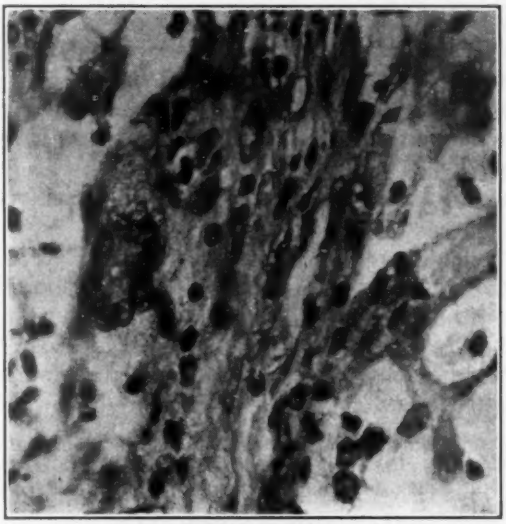

FIG. 5.—Giant cells (Touton-like) and foam cells.

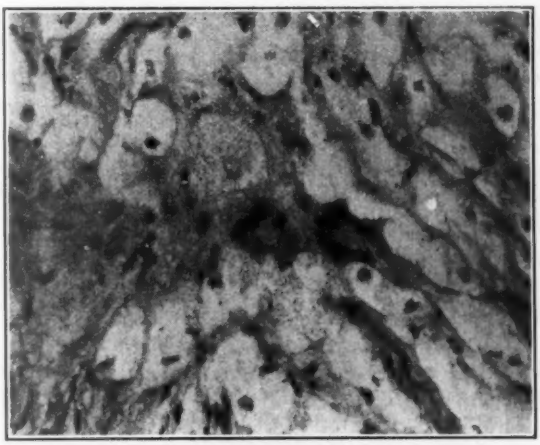

FIG. 6.—Giant cells (Touton-like) and foam cells.

A new Roentgen ray examination at the end of December, 1942, showed that the bony callosity was being slowly but aberrantly formed, giving, for the time being, an impression of fragility.

In no other part of the bony skeleton was any lacuna of rarefaction observed, the left tibia, however, showed greater permeability to the Roentgen rays, apparently a process of decalcification. We have tried to readjust the amounts of vitamins A and D as well as the supply of calcium in the food and the patient continues under observation.

Comment. Even if we restrict the use of the name Hand-Christian's disease to the morbid condition in which the classical triad of symptoms are present, *viz.* (1) multiple lacuna shadows in the cranial bones, (2) exophthalmia and (3) diabetes insipidus, the diagnosis of Hand-Christian's syndrome can be justified in our case by virtue of the presence of a rarefying osseous lesion of the left femur and diabetes insipidus, because this latter symptom leads us to suspect a lesion of the hypophysis although it has not yet been possible to demonstrate this radiologically.

The histologic examination of the material taken from the seat of fracture showd the existence of a granulomatous lesion which in a certain zone showed accumulation of eosinophils giving the picturè of eosinophil granuloma; in another zone there were lipophages (foam cells), arranged like a typical lipogranuloma.

The cellular hyperplasia and thickening of the reticulum were apparent in the preparations.

We thus arrive at the following conclusion:

Conclusion. In accord with Farber, Bass, Gross and Jacox, and based on our own observations, we are of the opinion that the clinical pictures referred to in this paper should be regarded as variations of the same morbid process, which in a more advanced stage is known as Hand-Christian's disease.

We are grateful for the invaluable collaboration of Prof. Oromar Moreira, Dr. A. C. Cavalcanti, Dr. Edgard A. Cerqueira and Dr. Paulo Rocha, who kindly carried out the chemical dosage and radiologic examinations, and to Prof. Ollivierre who made the translation into English.

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SULFONAMIDE INHIBITING ACTION OF PROCAINE

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The original method of Marshall[16] and its later modifications[2,6] for determining sulfanilamide depend on diazotization and the coupling of the resulting diazo compound to produce an azo dye which can be

easily estimated by colorimetric comparison. The reaction depends on the presence of an amino group substituted in the benzene ring and can, therefore, be used for the estimation of any derivative of sulfanilamide or for any related aromatic compound in which the amino group is free or can be freed by hydrolysis. Recognition of this fact has served to explain inconsistencies in the determination of sulfonamide drugs in body fluids.[3] Procaine ("novocaine"), which is the local anesthetic most commonly employed in obtaining such body fluids, is β-diethylaminoethyl-p-aminobenzoate[11] and thus has a free aryl amine which may enter this reaction. The procaine may contaminate the test fluid either from its presence in the needle and syringe or by admixture with the fluid withdrawn after procaine infiltration.[1,4,17] Failure to recognize this possibility is probably responsible for gross misinterpretations and erroneous results.[10,12] Other local anesthetics not derived from p-aminobenzoic acid do not have this interfering effect.[11,13,17]

Woods[23] was the first to demonstrate that p-aminobenzoic acid and related compounds, including procaine, exert a marked inhibiting effect on the bacteriostatic action of sulfanilamide on hemolytic streptococci *in vitro*. The inhibiting effect of procaine was found to be quantitatively similar to that of p-aminobenzoic acid but it was somewhat delayed, probably because the compound was hydrolyzed by the organisms. Sulfapyridine required 5 times as much p-aminobenzoic acid as was needed for sulfanilamide to produce the same degree of inhibition. This was interpreted as indicating that sulfapyridine was 5 times as active as sulfanilamide. Selbie,[19] at the same time, showed that this inhibiting action of p-aminobenzoic acid can also be demonstrated *in vivo* in mice infected with hemolytic streptococci and treated with sulfanilamide. Boroff, Cooper and Bullowa[1] estimated the average concentration of procaine in pleural fluid removed after the use of this agent to be 0.0002% (0.2 mg. per 100 cc.) and they showed that this amount was sufficient to inhibit *in vitro* the action of at least 0.005% (5 mg. per 100 cc.) of sulfapyridine on Type III pneumococci. Larger concentrations of urethrane, which is not a p-aminobenzoic acid derivative, did not exert this inhibiting effect. Similar observations on the inhibiting action of p-aminobenzoic acid compounds have been made both *in vitro* and *in vivo* with the same or other sulfonamides and with other organisms, including *E. coli*, *Staphylococcus aureus* and Type I pneumococcus.[13,15]

Casten, Fried and Hallman[5] have shown that in rabbits procaine inhibits the bacteriostatic action of sulfathiazole in wounds inoculated at the time of trauma with suspensions of *Staphylococcus aureus*. They concluded from their observations that procaine is contraindicated as a local anesthetic in the treatment of open wounds or compound fractures if sulfathiazole is to be used topically. DeWaal, Kanaar and McNaughtan[7] using hemolytic streptococcus infections in mice found that massive non-toxic doses of procaine given at short intervals were necessary in order to produce any significant antisulfanilamide action. They also cited 3 cases of human hemolytic strepto-

coccal and pneumococcal infections in which sulfapyridine was given orally and no discernible antisulfonamide action resulted from the local injections of procaine in amounts varying from 60 cc. of a 1% solution to 50 cc. of a 3% solution (0.6 to 1.5 gm.). The procaine was used, at least 24 hours after the sulfapyridine was started—for incision of infected wounds in 1 of these cases and to infiltrate the pleura for the relief of pain in the other 2 cases.

Legge and Durie[14] presented evidence that procaine is hydrolyzed to p-aminobenzoic acid by an esterase present in human blood and in mice. Among mice injected with hemolytic streptococci and treated with sulfanilamide, the injection of procaine caused a slight increase in the mortality rate. Although they presented no clinical data, they suggested that procaine and other local anesthetic agents of the p-aminobenzoic acid class are contraindicated when the patient is so seriously infected that even a slight delay in treatment with sulfonamides may diminish the chances of survival or when massive tissue damage is present and the circulation in the damaged tissue is poor so that the removal of p-aminobenzoic acid from the tissue after the use of procaine may be very slow.

Goldberg, Koster and Warshaw[9] showed that no appreciable concentration of procaine is built up in the blood during spinal anesthesia. Once it gets into the blood stream the procaine is rapidly hydrolyzed (detoxified) by an enzyme and some of the free amino group resulting from this hydrolysis is further acetylated by a less active enzyme and the products are rapidly excreted in the urine. An average of 90% of injected procaine is thus excreted in the urine but only in the form of the products of detoxification; these are more or less equally divided between p-acetaminobenzoic acid, p-acetaminohippuric acid and p-acetaminobenzoyl glycuronate.

In this laboratory[21] it has been shown that p-aminobenzoic acid given orally in humans is rapidly excreted in the urine, largely in conjugated form. This rapid excretion also occurs in mice and accounts for the necessity of using frequent and large doses of p-aminobenzoic acid to inhibit the action of sulfonamides, since the latter are excreted more slowly.[7,22]

The sulfonamide inhibiting effect of procaine thus seems well established insofar as it concerns bacterial growth in artificial media and, to a lesser extent, in experimental animals. In the latter, repeated injections of large doses of procaine seem to be essential when the sulfonamide is used to combat a general infection, but local infiltration with comparatively small doses of procaine seem to be sufficient to interfere with the action of sulfonamides applied topically for the prevention of wound infection. Thus far, little if any evidence has been brought forth to indicate that this sulfonamide inhibiting action of procaine is of significance in human infections. It is the purpose of this paper to present: 1, the results of studies which indicate that procaine as employed in local anesthesia, may inhibit the action of sulfonamides in human blood; and, 2, case reports illustrating the local sulfonamide-inhibiting action of procaine.

Experimental. *Materials and Methods.* The subjects for these studies were shown, in preliminary tests, to have little or no bactericidal action against the test organisms in their freshly shed defibrinated blood. Whenever possible, patients undergoing operations under local anesthesia with procaine were used in these studies. The stock strain of Type III pneumococcus was employed. The bactericidal tests with human blood were carried out as in previous studies.[20] Briefly, 0.5 cc. amounts of fresh defibrinated blood were placed in pyrex tubes; serial decimal dilutions of a fully grown culture were added in 0.1 cc. amounts and other ingredients were also added in a volume of 0.1 cc. The tubes were then sealed in a gas-oxygen flame and rotated slowly in an incubator at 37.5° C. The tubes were observed for growth as indicated by color change at 24 and 48 hours and by cultures of the blood in the tubes which failed to show a color change. When human serum was used, sterile glucose was added to a final dilution of 0.1% and growth was observed grossly or bacterial counts were done by making blood agar pour plates with dilutions of the resulting growth at the end of appropriate periods of incubation.

Chemical determinations of sulfonamide levels were made by the method of Bratton and Marshall[2] using a photoelectric colorimeter. The same method was used for the determination of procaine. When the blood contained both these chemicals, the total color change was read only with reference to the sulfonamide.

Antisulfonamide Action of Procaine in Human Blood, in vitro. It was shown in preliminary studies that the concentration of procaine obtained in the blood of patients undergoing local anesthesia in which a total of 0.5 to 2.5 gm. was used, ranged from 0.5 to 1.7 mg. per 100 cc. of the free procaine (namely, that portion circulating with a free aryl amine) with about an equal amount conjugated (probably acetylated on the amino group). Tests were, therefore, made *in vitro* with concentrations of procaine ranging from 0.1 to 1.5 mg. per 100 cc. and with amounts of sulfadiazine up to 20 mg. per 100 cc. The results of an experiment with Type III pneumococci in human blood are shown in Table 1. Procaine in concentrations of 1 mg. per 100 cc. or higher had a marked inhibiting effect in the bacteriostatic action of sulfadiazine in concentrations as high as 20 mg. per 100 cc. Smaller concentrations of the procaine had a moderate inhibiting effect on the action of smaller amounts of the sulfonamide.

TABLE 1.—EFFECT OF PROCAINE *in vitro* ON THE BACTERIOSTATIC ACTION OF SULFADIAZINE IN HUMAN BLOOD

Added to 0.5 cc. defibrinated blood			Added to 0.5 cc. defibrinated blood		
Sulfadiazine*	Procaine*	Bacteriostasis†	Sulfadiazine*	Procaine*	Bacteriostasis†
0	0	0	10	0.1	87,000
			10	0.5	870
2.5	0.1	87,000	10	1.0	0
2.5	0.5	87	10	1.5	0
2.5	1.0	0			
2.5	1.5	0	15	0.1	87,000
			15	0.5	870
5	0.1	87,000	15	1.0	0
5	0.5	87	15	1.5	0
5	1.0	0			
5	1.5	0	20	1.0	0
			20	1.5	0

* Mg. per 100 cc.

† Largest number of Type III pneumococci which failed to show visible growth in 48 hours; in this column 0 = less than the smallest inoculum used (8 or 9 diplococci).

Antisulfonamide Action of Procaine in Human Serum in vitro. The results of one of a number of experiments are shown in Table 2. In this experiment sulfathiazole was used in concentrations up to 40 mg. per 100 cc. Here again, procaine in a concentration of 1 mg. per 100 cc. or higher permitted the free multiplication of Type III pneumococci in the presence of concentrations of sulfathiazole as high as 40 mg. per 100 cc. and 0.1 mg. of procaine per 100 cc. inhibited the action of 10 mg. per 100 cc. of sulfathiazole.

TABLE 2.—EFFECT OF PROCAINE *in vitro* ON THE BACTERIOSTATIC ACTION OF SULFATHIAZOLE IN HUMAN SERUM

0.5 cc. serum + 6600 Type III pneumococci +

Sulfathiazole (mg./100 cc.)	Procaine (mg./100 cc.)				
	0	0.01	0.1	1.0	2.5
0	+	+	+	+	+
10	0	0	+	+	+
20	0	0	0	+	+
30	0	0	0	+	+
40	0	0	0	+	+

+ = heavy growth in 48 hours, 0 = no visible growth.

The following studies were carried out with blood obtained from human subjects in whom procaine was used either for local anesthesia in operative procedures or by subcutaneous or intramuscular injection given specifically for this purpose.

TABLE 3.—EFFECT OF PROCAINE *in vivo* ON THE BACTERIOSTATIC ACTION OF SULFADIAZINE IN HUMAN BLOOD

		Blood taken		
		Before sulfadiazine	Before procaine	After procaine
Subject A.	Bacteriostasis* . .	Less than 8	8,200	8
	Sulfadiazine content†	0	F 7.3	F 7.7
			T 8.4	T 8.4
Subject B.	Bacteriostasis* . .	25	25,000	250
	Sulfadiazine content†	0	F 9.9	F 11.7
			T 11.8	T 14.6
Subject C.	Bacteriostasis* . .	4	44,000	44
	Sulfadiazine content†	0	F 8.1	F 7.9
			T 10.9	T 11.6

* Largest number of Type III pneumococci which failed to give visible growth in 48 hours.

† The sulfadiazine concentration (in mg. per 100 cc.). This includes procaine or its hydrolyzed product. On the basis of other observations the procaine should account for 0.5 to 1.7 mg. per 100 cc. (free). F = free. T = total.

A received 3 gm. of sodium sulfadiazine intravenously 3 hours before the procaine infiltration which took 30 minutes. The last blood was taken 40 minutes after a total of 2 gm. of procaine.

B received 2.5 gm. of sodium sulfadiazine intravenously 3 hours before procaine injection. A total of 2 gm. of procaine was injected subcutaneously in 30 minutes and blood was taken 1 hour later. (3 hours thereafter the blood level (calculated as sulfadiazine) was 9.5 mg. per 100 cc. free and 12.4 mg. per 100 cc. total, and 25,000 organisms were killed).

C received 3 gm. of sodium sulfadiazine intravenously 3½ hours before an intramuscular injection of 1 gm. of procaine in 30 cc. of saline and blood was obtained ½ hour later. After another 1½ hours the same number of organisms were killed and the blood level was 7.7 mg. per 110 cc. free and 11.6 mg. per 100 cc. total.

Effect of Procaine, in vivo, *on the Action of Sulfadiazine in Human Blood.* The results of studies in 3 patients are shown in Table 3.

Each of these subjects received an intravenous injection of sulfadiazine prior to the procaine injection. Blood was taken before each of the procedures and again at intervals after the injection of procaine. The greatest amount of inhibition was usually found to occur between ½ and 2 hours after the injection of procaine was completed. In each of these cases, although the exact amount of procaine in the blood was not determined, it is obvious that a marked inhibiting effect was exerted by the procaine on the antipneumococcal action of the sulfadiazine in the blood.

Similar experiments were carried out with sulfathiazole. With levels of this drug ranging from 2 to 4 mg. per 100 cc. injections of procaine totaling up to 1 gm. had only a slight inhibiting effect in some cases and none in others.

Effect of Procaine in vivo *in Human Serum.* A number of studies were made with serum obtained from patients who had received procaine injections. The effect of the procaine in the serum on the bacteriostatic action of added sulfathiazole was studied by bacterial counts made after varying periods of incubation. The result of one of these experiments is shown in Table 4. The concentration of "free" procaine was found to be 1.7 mg. per 100 cc. This amount of procaine had a definite inhibiting effect on the bacteriostatic action of sulfathiazole in concentrations as high as 25 mg. per 100 cc.

TABLE 4.—INHIBITING EFFECT OF PROCAINE *in vivo* ON THE BACTERIOSTATIC ACTION OF SULFATHIAZOLE ADDED TO HUMAN SERUM

Sulfathiazole added (mg./100 cc.)	Organisms per cc. after 48 hours growth in serum obtained	
	Before procaine	After procaine*
0	3,450,000,000	2,200,000,000
5	900,000,000	1,490,000,000
10	11,000,000	2,780,000,000
15	950,000	2,100,000,000
25	97,000	1,610,000,000

* Inoculum, 8300 organisms per cc. of serum. Concentration of procaine per 100 cc. of serum: 1.7 mg. free, 3.3 mg. total. This serum was obtained from blood drawn ½ hour after subcutaneous injection of 1.5 gm. of procaine (without adrenalin).

Cases Illustrating Local Inhibition of Sulfonamide Action by Procaine. The results of the foregoing studies indicate that when procaine is used for local anesthesia in operative procedures (such as herniorrhaphies or operations on the gall bladder), or when equivalent amounts of this drug are injected subcutaneously or intramuscularly, concentrations of procaine or of derivatives containing a free aryl amine are absorbed into the blood in sufficient concentration to inhibit the bacteriostatic action of large concentrations of sulfadiazine or sulfathiazole. That procaine injections may permit the development of infection at the site of infiltration even while adequate concentrations of sulfonamides are maintained in the body, is illustrated in the following cases. Only the relevant details of these cases are presented.

Case Studies. CASE 1. This is one of the first cases of pneumococcal meningitis with recovery observed at the Boston City Hospital and many of the details have been reported elsewhere.[8] In this case, fever and symptoms of

meningitis appeared 2 weeks after the partial removal of a posterior fossa tumor in November, 1937. Sulfanilamide therapy was started at that time and continued over a period of about 9 weeks, a dose of 6 gm. daily being given during most of the first 6 weeks and 4 gm. daily thereafter. Blood levels of about 10 mg. per 100 cc. were maintained most of this time. Occasional lumbar punctures had been done during the first 2 weeks following the operation for drainage and for the relief of increased pressure. After purulent cerebrospinal fluid infected with Type 17 pneumococci was obtained, however, lumbar punctures were done 3 or 4 times daily. Procaine, 1 to 2 cc. of a 2% solution, was used for local infiltration of the skin and subcutaneous tissues prior to each puncture. Positive cerebrospinal fluid cultures were obtained intermittently during the first 10 days but the fluids obtained during the following 3 weeks were all sterile. During the last week of this period, the subcutaneous tissues over the 3d, 4th and 5th lumbar spaces, particularly the 4th, became soggy and tender. These were the spaces which had been used for the puncture. Increasing difficulty was encountered in entering the subarachnoid space due to underlying induration, but a free flow of clear fluid was obtained each time after the dura was entered. A sinus tract developed along the 4th lumbar space and this drained pus from which Type 17 pneumococci were obtained on culture. Fortunately, no epidural abscess developed and the cerebrospinal fluid did not become infected. When further punctures in this space were avoided, healing gradually occurred while sulfanilamide therapy was being continued. The patient was discharged much improved at the end of the 12th postoperative week.

CASE 2. A 67 year old man was admitted to the hospital in November, 1940, 10 days after a head injury. He was found to have purulent meningitis, and Type 19 pneumococci were obtained from cultures of blood and cerebrospinal fluid at entry. Treatment with sulfapyridine was begun promptly with an intravenous injection of its sodium salt followed by oral doses. Blood sulfapyridine levels were maintained at 9 to 11 mg. per 100 cc. during the 1st week and between 5 and 9 mg. thereafter. In addition, the patient received 330,000 units of Type 19 antipneumococcus rabbit serum on the day after entry.

Lumbar punctures were done daily during the first 12 days and again during the 4th week. Procaine, 2% solution, was used each time for infiltration of the skin and underlying tissues down to the dura. Blood cultures became negative but spinal fluid cultures continued to be positive for 6 days during which the protein content and leukocyte counts dropped steadily and the sugar level reached and remained normal. From the 7th to the 19th day cisternal fluid was sterile. On the 4th day the back over the site of the lumbar punctures became red and indurated and this gradually extended as a cellulitis to involve a large area of the back. Culture of the wound at the 4th lumbar space yielded Type 19 pneumococci.

The patient remained afebrile for about 10 days and seemed generally improved so the sulfapyridine was discontinued. Fever then recurred, as did the infection of the back, and the drug therapy was resumed after 3 days. During this time signs of meningitis also recurred and both the blood and cerebrospinal fluid cultures again became positive and its sugar content dropped. In spite of continued therapy with sulfapyridine and later with sulfadiazine, both orally and parenterally, the patient's fever and infection persisted and the patient died at the end of the 5th week.

CASE 3. A 66 year old man was admitted to the hospital in February, 1942, after a 4 weeks illness and was found to have an extensive but apparently resolving lobar pneumonia and purulent meningitis. Type 25 pneumococci were obtained from cultures of the blood and cerebrospinal fluid at the time of entry. Treatment with sulfadiazine was begun promptly and continued for 5 weeks during which the concentration of the drug in the blood was maintained between 10 and 15 mg. per 100 cc. In addition, 240,000 units of Type 25 antipneumococcus rabbit serum was given intravenously on the day after admission.

Lumbar punctures were done twice daily during the first 3 days, chiefly

for the relief of increased intracranial pressure, and at greater intervals thereafter to observe the progress of the meningeal infection. Procaine in a 2% solution was used each time to infiltrate the skin and underlying tissues down to the dura. Blood cultures taken on the day after entry and later were all sterile. Cultures of all the cerebrospinal fluids obtained during the first 48 hours were positive and subsequent ones obtained during the next 11 days showed no growth. During this time the protein and cellular content dropped almost to normal and the level of the sugar rose to normal and remained so for over a week.

At the end of the second week in the hospital when the temperature, pulse and white blood cell count had been normal for 10 days and the lungs had completely cleared, another lumbar puncture was done. The fluid was clear and colorless with a protein content of 62 and sugar of 46 mg. per 100 cc. and a leukocyte count of 50 cells per c.mm., of which 40 were lymphocytes. Culture of this fluid, however, yielded Type 25 pneumococci. It was then noted that there was a small, red, indurated area under the skin at the 5th lumbar space where all of the punctures had been done. Another puncture done in the 3d lumbar space after this result was obtained yielded fluid which was sterile, although para-aminobenzoic acid had been added to the culture medium. At this time and after subsequent punctures 1% sodium sulfadiazine in physiologic salt solution was injected along the path of the needle as it was withdrawn. The local lesion cleared and there was no further evidence of infection. The patient was discharged improved after an additional 6 weeks of observation.

Case 4. A 16 year old girl was admitted to the hospital Nov. 11, 1941, with a history of a chill followed by fever, prostration and pleuritic pain of 1 day duration. The physical signs in the chest were consistent with fluid in the right pleural cavity, and the white blood cell count was 29,000 per c.mm. Sulfathiazole therapy in full doses was started promptly and continued without interruption for 5 weeks. During this time the blood levels of free sulfathiazole ranged between 2.2 and 4.1 mg. per 100 cc. in spite of additional doses of 3 gm. each of sodium sulfathiazole, intravenously given on several days.

A thoracentesis was attempted on the day after admission but yielded no fluid from three different sites. On the 6th day, however, another chest tap yielded 5 cc. of yellowish-green, odorless pus from which hemolytic *Staphylococcus aureus* was obtained in abundance and in pure culture. On the following day 15 cc. of similar fluid was obtained from a second tap. Procaine was used to infiltrate the skin and underlying tissues down to and probably including the parietal pleura at each point. During the next 3 days, small abscesses developed at the site of each of the puncture wounds and extended deep into the subcutaneous tissues. On the 11th day a thoracotomy and rib resection was performed with 1% pontocaine (which is not a p-aminobenzoic acid derivative) for local anesthesia. In addition to the abscesses in the thoracic wall, many loculated cysts were found extending into the interlobar fissure and down to the diaphragm. All contained thick pus from which *Staphylococcus aureus* was cultured. The pockets were broken up into a large single cavity into which 10 gm. of powdered sulfadiazine was scattered and an iodoform gauze pack inserted.

Cough productive of purulent sputum, fever and leukocytosis continued for another 4 weeks during which the cavity decreased in size. The patient was discharged at the end of the 8th week with a small healing cavity.

Comment. In each of the first 3 cases, procaine was repeatedly injected into the same areas. Infection, apparently conveyed from the subarachnoid space, developed along the track of the needle that was used to penetrate the dura. This infection developed in spite of the continuous presence in the body of bacteriostatic concentration of sulfonamide drugs. That effective sulfonamide bacteriostasis was maintained throughout the rest of the body at the time is

indicated in Cases 1 and 3 by the fact that there was no evidence of active infection of the spinal fluid when the organisms were obtained from the tissues and also by the failure of reinfection to occur when the dura was penetrated by the needle which had passed through the infected tissues. It is fair to assume that the sulfonamide bacteriostasis was inhibited in the tissues locally by the high concentration of procaine that was present at the site of infiltration and that this inhibiting action lasted long enough for infection to become established in that area. In Case 2 the local infection of the skin and subcutaneous tissues was extensive and may have been a source of reinfection.

In Case 4 infection with a hemolytic *Staphylococcus aureus*, which is generally less amenable to sulfonamide therapy, became established at each of the sites where procaine infiltration was carried out in attempting to do a thoracentesis. Infection from the underlying lung or pleura became established along the track of the thoracentesis needle in each instance.

This complication of procaine anesthesia may be avoided in one of two ways: either (1) a different drug may be used which is not of the p-aminobenzoic acid series[11,13] and that will not have the sulfonamide inhibiting effect; or (2) a small amount of sulfonamide drug may be injected from a different syringe through the same needle while it is being withdrawn. For most sulfanilamide derivatives 0.5 to 1% solution of the sodium salt in physiologic saline will serve the purpose.

With respect to the systemic sulfonamide inhibiting action of procaine absorbed from an area of local infiltration, it is fair to assume that this effect is not significant clinically except in rare cases. Procaine like p-aminobenzoic acid[21] is conjugated in the body and it is excreted in the urine in both the free and conjugated forms at a much more rapid rate than are any of the effective sulfonamides now in general use. This inhibiting action should, therefore, be of importance only in patients with severe infections in whom a delay of a few hours in the effective action of a sulfonamide drug may be crucial. When used in spinal anesthesia, the amount of procaine absorbed into the circulation and present in a form in which it might have an antisulfonamide action is probably very small indeed.[9] The high concentration of the free procaine in the spinal fluid, however, may be of importance, particularly if infection is accidentally introduced.

Conclusions. Procaine, in amounts ordinarily employed for local anesthesia, may be absorbed into the circulation in sufficient concentration to exert a definite inhibiting effect on the action of sulfonamide drugs that may be present in the blood.

Infection introduced into an area which has been infiltrated with procaine may become established locally in spite of the continuous presence in the body of bacteriostatic concentrations of sulfonamide drugs.

It is desirable to use local anesthetic drugs other than p-aminobenzoic acid derivatives for infiltration when performing exploratory punctures of potentially infected areas. Procaine, or similar anesthetics of the p-aminobenzoic acid series should also be avoided in extensive

operative procedures on patients having severe infections in which rapid and effective action of sulfonamide drugs is essential.

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THE TOXICITY OF SULFADIAZINE

Observations on 1357 Cases

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The greater clinical value of sulfadiazine over the other commonly used sulfonamide drugs depends in great measure upon its relatively lower degree of toxicity.[2–4] It has seemed important to us to record and evaluate the toxic reactions that have appeared in the patients treated with sulfadiazine or sodium sulfadiazine on all of the services at The New York Hospital. The chief advantage of this study is that every patient was seen daily by physicians on the alert for the occurrence of sulfonamide reactions, and the recognition of signs of toxicity was further aided by a hospital routine which included in almost all cases daily measurement of fluid intake and output, blood count,

urinalysis, and blood sulfadiazine determination. In addition there were frequent other blood chemical studies, routine Roentgen ray and bacteriologic procedures, and in many cases urologic and dermatologic consultations. We feel that very few toxic reactions were overlooked; on the other hand, all reactions included were well substantiated.

To May 1, 1942, we observed a total of 1357 patients treated with a daily dosage of 3, 4 or 6 gm. of sulfadiazine* orally over a period of 2 days or more, or with at least 2.5 gm. or more daily of sodium sulfadiazine intravenously. Of these, 1113 received sulfadiazine orally and 244 received sodium sulfadiazine intravenously, either alone or supplementary to sulfadiazine by mouth. Of the patients receiving oral sulfadiazine, therapy lasted between 2 and 14 days in 973. However, 120 patients received sulfadiazine for more than 2 weeks, and 18 patients for more than 4 weeks. Twenty-nine patients each had more than 8 injections of sodium sulfadiazine intravenously. Patients of all ages were included (Table 2). Of the 1113 patients who were given sulfadiazine orally, 912 received a daily dosage of 6 gm., 86 received 4 gm., and 115, 3 gm. The infants and children included in this study were given a daily dosage of at least 0.1 gm. of sulfadiazine or sodium sulfadiazine per kilogram of body weight and therefore are included with the adults on the 6-gm. daily dosage. The 244 patients who were given sodium sulfadiazine intravenously received 2.5 gm. (10 cc. of 25% solution) every 8 to 24 hours, the time interval depending upon whether sodium sulfadiazine was used alone or supplementary to oral therapy.

Important factors which might be expected to influence the occurrence of toxic reactions are: (1) Daily dosage of drug. (2) Presence or absence of previous sulfonamide therapy (or previous reactions to the sulfonamides). (3) Total dose of drug and the length of time during which the drug is administered. (4) Route of administration. (5) Age of patient. (6) Presence or absence of impaired renal function. (7) Fluid balance. (8) pH of the urine.

Before determining the influence of these different factors, a baseline for the toxicity of sulfadiazine was created by ascertaining the incidence and severity of reactions under the most usual conditions of therapy—those that most often prevail in the hospital in the treatment of such conditions as pneumonia, meningitis, and puerperal and surgical infections. It is to be particularly noted that adjuvant alkali therapy was not given to these patients as a prophylactic measure against renal reactions. This treatment was instituted later and has proven effective in preventing renal reactions.[5,6] An analysis of these later cases compared with those included in this paper is being made separately.[7]

Toxicity Under Usual Conditions of Therapy. We found that there were 705 individual patients in our series (Column 3 of Table 1) who had received an oral dosage of sulfadiazine of 2 or 4 gm. initially, followed by 1 gm. every 4 hours continued for not less than 2 days or

* The sulfadiazine for most of these patients was kindly supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

more than 14 days, none of whom had had sulfonamide therapy previously and none of whom received sodium sulfadiazine intravenously. Patients of all ages were included in this group. The fluid output in most of these patients was well maintained; none of the patients had serious impairment of renal function.

Of the 705 patients, 62 (8%) exhibited some definite evidence of toxicity to sulfadiazine. The corollary, of equal interest and significance, is that 643 (92%) of the patients treated orally with a full therapeutic dosage of sulfadiazine showed no recognizable toxic manifestations. The much lower incidence of minor toxic effects following sulfadiazine are also impressive, as compared with those of sulfanilamide, sulfapyridine, or sulfathiazole. Practically all patients taking sulfapyridine are made "sick" by the treatment; if they are not severely nauseated and vomiting, at best they have no appetite, appear pale and gray, and are depressed and unhappy. During therapy with sulfanilamide and sulfathiazole, although severe vomiting is much less common than with sulfapyridine, the patients are frequently off-color and depressed, complaining commonly of nausea, headache, or other symptoms. The patient on sulfadiazine therapy is usually totally different. He usually takes the drug without the slightest complaint; nausea or loss of appetite is rare, his color is normal, he is not depressed. Long[12] has recently stated that the frequency of important toxic reactions following sulfadiazine is only 6.5% as compared with 11.9% following sulfanilamide, 15.9% following sulfapyridine, and 18.6% following sulfathiazole.

The most common toxic effect following sulfadiazine in the 705 patients (Table 1, Column 3) was renal irritation. This reaction occurred in 34 patients (4.8% of the group). Its significance becomes obvious when it is noted that of the 62 patients who showed signs of toxicity, 34 had those of renal irritation. Two of the 34 patients had fever also, and 1 both fever and a rash. Drug rash and fever occurred 14 times (2% of the 705 patients). Therefore, in this large series only 15 patients (2%) had any reaction other than renal irritation or rash and fever. The rise in temperature accompanying the drug rashes was sometimes only slight. Drug fever alone was recognized only once. A definite drop in the total number of white blood cells below 3000 per c.mm. or in the granulocytes below 35% was observed in 6 cases, but in none of these did the total white count fall below 2000 per c.mm., or the percentage of granulocytes below 10. In none of the patients were changes in the red blood cells recognized. In 1 of the surgical cases, however, a severe thrombocytopenia resulting in death occurred following 6 days of treatment with sulfadiazine in a dosage of 6 gm. daily. This was the only fatal toxic reaction in the total group of 1357 patients.* Severe nausea and vomiting occurred 5 times, and there was 1 case of conjunctivitis and 1 of severe headache and vertigo.

* Since this paper was written, an additional 1496 patients have been treated in The New York Hospital with sulfadiazine orally or sodium sulfadiazine intravenously without another fatality in the 2853 cases treated to date.

TABLE 1.—TOXIC REACTIONS AFTER SULFADIAZINE THERAPY

	Oral sulfadiazine—1113 patients						
			2 or 4 gm. initially, followed by 6 gm. daily*				
			2 to 14 days inclusive				
Reaction	3 gm. daily* 115 patients 1	4 gm. daily* 86 patients 2	No previous sulfonamides 705 patients 3	Previous sulfonamides 87 patients 4	Over 14 days 120 patients 5	Sodium sulfadiazine I.V., with or without sulfadiazine orally* 244 patients 6	Total 1357 patients 7
Renal reaction	..	4	31	4	3	16	58
Renal reaction with drug fever	..	..	2	..	..	..	2
Renal reaction with rash and fever	..	..	1	..	..	2	3
Drug rash and fever	..	..	13	2	2	2	19
Drug rash with leukopenia	..	..	..	1	..	..	1
Drug rash with peripheral neuritis	..	..	..	..	..	1	1
Drug rash with stomatitis	..	..	..	..	..	1	1
Leukopenia and/or granulocytopenia	..	1	6	2	4	2	15
Drug fever alone	1	..	1	1	1	..	4
Nausea and vomiting	..	2	5	..	..	2	9
Thrombocytopenia	..	..	1†	..	..	..	1†
Jaundice—possible hepatitis	..	..	..	..	..	2	2
Conjunctivitis	..	..	1	..	..	..	1
Stomatitis	..	..	..	..	..	1	1
Headache and vertigo	..	..	1	..	..	..	1
Encephalopathy	..	..	..	..	..	1	1
Arthralgia	..	1	..	..	..	..	1
Total patients with reactions	1	8	62	10	10	30	121
Per cent with reactions	0.8	9.2	8.0	11.5	8.3	12.3	8.9
Summary							
Total patients with renal reactions	..	4 (4.7%)	34 (4.8%)	4 (4.8%)	3 (2.5%)	18 (7.4%)	63 (4.6%)
Total patients with drug rash	..	..	14	3	2	6	25
Total patients with drug fever	1	..	3	1	1	1	7
Total patients with W.B.C. effects	..	1	6	3	4	2	16
Total patients with misc. reactions	..	2	8	..	..	8	18

* All patients treated for at least 2 days.
† This was the only fatal toxic reaction in the series.

Influence of Daily Dosage of Drug. For an evaluation of the rôle played by daily dosage of drug upon the toxicity of sulfadiazine, we have for comparison with the 6-gm. per day series 2 groups of cases, each treated with a lower dosage. In 1, the patients received 4 gm. daily (Table 1, Column 2), and in the other, 3 gm. daily (Column 1). The 86 patients given 4 gm. each day showed approximately the same percentage of reactions as did those who were given 6 gm. daily. However, it happened that none of the 86 patients developed a drug rash, and there was 1 case of arthralgia, which is one of the rare toxic conditions due to sulfonamide therapy.

That the incidence of toxic reactions is influenced by the daily dosage of sulfadiazine is indicated, however, by the fact that in 115 hospital patients receiving 3 gm. per day there was only one toxic reaction, a moderately severe drug fever that occurred on the 10th day of therapy and without previous use of the sulfonamides. Further evidence that there is a very low degree of clinical toxicity following a

3-gm. per day dosage of sulfadiazine comes from our observations on approximately 200 ambulatory patients not included in Table 1. Each of them received the 3-gm. amount for a period of 4 days and had at least 1 urinalysis and 2 blood counts during the time of therapy. In this group we discovered 1 case of mild granulocytopenia and 3 of mild renal irritation. While these findings show a very low degree of toxicity, they also indicate that reactions can occur with such a low dosage of sulfadiazine, and they present another warning against the overenthusiastic and careless use of the sulfonamides.

Concentration of Sulfadiazine in the Blood. The toxic reactions in 1155 patients who had frequent measurements of blood levels have been analyzed according to the concentration of drug in the blood. Of 117 patients showing less than 5 mg. per 100 cc. of sulfadiazine in the blood, 1.8% developed toxic reactions; of 505 having 5 to 10 mg. per 100 cc. concentration, 7% showed reactions; of 371 with 10 to 15 mg. per 100 cc., 12.8% had toxic symptoms; and of 162 patients with more than 15 mg. per 100 cc., 14.8% showed evidences of toxicity.

The 3-gm. daily dosage of sulfadiazine gave concentrations in the blood of 5 mg. per 100 cc. or less in 46% of the patients, of 5 to 10 mg. per 100 cc. in 36%, of greater than 10 mg. per 100 cc. in 18%. The corresponding values for the 4-gm. daily dosage were only slightly higher. On the other hand, with the 6-gm. daily dosage the concentration in the blood was less than 5 mg. per 100 cc. in only 5.8%, between 5 and 10 mg. per 100 cc. in 48.7%, and greater than 10 mg. per 100 cc. in 45.5%.

The Effect of Previous Sulfonamide Therapy. Our observations confirm those of Finland and his co-workers[3] and do not prompt the degree of concern that has been registered by some clinicians[13,17] regarding the dangers of repeated courses of sulfonamide therapy. Eighty-seven of our patients given 6 gm. of sulfadiazine daily had had previous sulfonamide treatment (Table 1, Column 4), and 10 of them (11.5%) had reactions, compared with 8% of the 705 patients similarly treated but without sulfonamides at a previous time. This increased incidence of toxic reactions seems to be significant because of the slightly higher incidence of drug rash and white blood cell effects; the incidence of renal complications was the same in both series.

We have observed a variety of relationships between reactions and previous sulfonamide treatment. For example, 1 patient developed an acute febrile reaction after a test dose of each of the sulfonamides: sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. In another patient, first sulfapyridine, then sulfathiazole, and finally sulfadiazine produced a drug rash and fever. In the case of drug rashes, fever, and blood dyscrasias, a possible sensitization phenomenon is more likely than in the case of a reaction such as a renal complication, which is apparently most frequently, if not always, of a mechanical or chemical nature.

Our cases show a few instances in which sulfadiazine was well tolerated by patients who had previously manifested toxic effects from sulfathiazole, and many examples of a similar type when sulfadiazine

was administered to patients who had shown a marked intolerance to sulfanilamide or sulfapyridine. The reverse of this—tolerance to the other sulfonamides after intolerance to sulfadiazine—occurred but was less common.

No definite rules can be made for subsequent sulfonamide treatment in patients who have exhibited evidences of intolerance to sulfonamides, except that in such cases one always must be doubly cautious. It is true that most of the fatalities following the sulfonamides have occurred after some unheeded warning. In 1 instance, a patient treated with sulfathiazole had had a drug rash and fever 2 weeks before the occurrence of acute agranulocytosis and death. Another case, reported in a previous communication,[14] of fatal aplastic anemia and toxic hepatitis following sulfapyridine was preceded several weeks by drug fever. Many such cases might be cited. We have, on the other hand, treated with great caution but successfully patients with past records of granulocytopenia, rashes, and fever following the sulfonamides. In most instances there has been no repetition of the previous reaction. This practice is dangerous and should be avoided except where the treatment is urgent.

Total Dose of Drug and Length of Time Administered. One hundred and twenty patients were treated with sulfadiazine for more than 14 days (Table 1, Column 5), with 8.3% of reactions compared with 9.1% in the entire group of 792 patients receiving the same daily dosage of sulfadiazine but for less than 14 days (Columns 3 and 4). Drug rash, drug fever, and toxic effects on the white blood cells rarely occurred before the 5th day of either oral or intravenous treatment. Following oral therapy, renal irritation rarely occurred before the 4th day, but following sodium sulfadiazine intravenously it often appeared on the 2d or 3d day, and in 1 instance on the 1st day. Our data do not suggest that the patient who has been receiving the drug for more than 3 to 4 weeks is safe from toxicity, as has sometimes been stated, any more than that a short course of therapy is entirely safe. An important rule to follow in the use of the sulfonamides is to discontinue the drug as soon as the danger of toxicity outweighs its usefulness. It is true that in an individual case the longer the drug is continued the greater is the chance of reaction in that case. It is not good practice to continue sulfonamide therapy indefinitely in obscure infections in which the value of the drug is at best questionable.

We have treated patients for exceptionally long periods of time. One patient with subacute bacterial endocarditis received a total dosage of 1333 gm. of sulfadiazine, and 4 others with the same condition received between 400 and 500 gm. continuous treatment with decreasing dosage of drug extending for periods as long as 4½ months. These patients who received the drug over periods of several months did not show any unusual toxic manifestations due to the prolonged treatment.

Route of Administration of Drug. The use of the sodium salt of sulfadiazine intravenously has been a life-saving measure in many of the patients who have been unable to take sulfadiazine orally or have been in desperate need of immediate optimal treatment, but the

dangers of toxic reactions are greater. In 244 patients who were given 1 or more intravenous injections, 30 (12.3%) had some form of reaction as compared with 8.9% of reactions in 912 patients treated orally with 6 gm. daily. More striking than the difference in the total reactions is the difference in the renal reactions with 18 occurrences (7.4%), in the 244 patients treated intravenously, as compared with 41, (4.5%) in 912 patients treated orally. Also, there were 2 cases of mild and transitory jaundice with possible toxic hepatitis probably attributable to the intravenous therapy, whereas in the 912 cases of oral therapy there was no such occurrence.

Age of Patient. The age distribution of patients having toxic reactions is shown in Table 2. The most significant finding is a lowered incidence of reactions in the group less than 1 year of age. A greater tolerance for the sulfonamides by infants than by adults has been suggested. According to our analysis, the decreased incidence of total toxicity in infants is accounted for by a low incidence of renal reactions. Whether renal complications are less frequent in infants, or are not readily recognized, cannot be stated. Conceivably, increased alkalinity of the urine of infants compared with the urine of adults may result from dietary differences or more frequent vomiting, thereby reducing renal toxicity.

TABLE 2.—AGE DISTRIBUTION OF PATIENTS WITH TOXIC REACTIONS

Age in years	No. of patients	No. of patients with reaction	Percentage with toxic reaction
0– 1	127	5	3.9
1– 5	82	8	9.8
5–10	44	6	13.6
10–20	100	14	14.0
20–60	805	72	8.9
60–80	199	16	8.0
	1357	121	

Renal Reaction and the Influence of Impaired Renal Function, Fluid Balance, and pH of Urine. Our table shows that following sulfadiazine therapy, renal irritation is by far the most common reaction, occurring in 4.6% of all cases, and meaning that more than half of all the patients having any reaction at all have a renal complication. This toxic reaction is especially common after intravenous sodium sulfadiazine, occurring in 7.4% of all the patients treated. Recent publications have also emphasized the importance of this reaction and have described a number of resultant fatalities.[1,8,9,11,15,16]

The particular manifestations of renal irritation in the 63 patients in whom this reaction was observed are shown in Table 3. Nineteen patients had microscopic hematuria alone which could be accounted for only on the basis of the sulfonamide therapy. Nine patients had grossly blood urine. Pain alone occurred in 8 patients. In 13 cases pain was accompanied by microscopic hematuria and in 10, by gross hematuria. The distribution of oliguria in respect to other evidences of renal complication is listed in Table 3. The renal pain experienced was of several types. More commonly it was flank pain and tenderness

similar to that of renal infarct. Typical ureteral colic occurred in some of the cases, and in a few the pain and tenderness were of a severe, generalized abdominal type suggesting appendicitis or mesenteric thrombosis. Oliguria was definitely recognized 7 times, and was most common when the other symptoms were most severe, although in 1 instance it occurred without any other finding. Anuria developed in only 2 cases, and in neither of these did it exist for more than 24 hours. All of our patients who experienced renal complications recovered without treatment other than cessation of sulfadiazine therapy, forcing of fluids, and administration of alkali. In no instance was it necessary to resort to ureteral catheterization and lavage. None of the patients who had histories of renal complications from sulfadiazine has been found to have any permanent renal impairment due to the sulfadiazine therapy.

TABLE 3.—MANIFESTATIONS OF RENAL IRRITATION

	No. of patients	No. with oliguria
Microscopic hematuria	19	0
Gross hematuria	9	2
Pain	8	1
Pain and microscopic hematuria	13	1
Pain and gross hematuria	10	2
Oliguria only	1	1
Total	63	7

Seven of the 63 patients who had had renal irritation later die of other causes and were examined at necropsy. Of these, 6 showed renal lesions attributable to the toxic effect of sulfadiazine, consisting of concretions of drug in the renal pelves and deposits of drug within the renal parenchyma with tubular degeneration and associated interstitial inflammatory reaction and occasionally secondary degeneration of the nephron. The kidneys of 39 patients who died during or soon after treatment with sulfadiazine, in whom renal irritation had not been recognized during life, were also examined at necropsy and pathologic changes like those described above were observed in only 3. In none of the 9 patients who showed at necropsy renal damage attributable to sulfadiazine were the lesions sufficiently extensive to justify the belief that permanent and serious impairment of renal function would have ensued had the patient lived.

While impaired renal function may have an influence upon the incidence and seriousness of renal reactions following the use of sulfonamides, of greater clinical importance is the effect of sulfonamide irritation of the urinary tract upon the prognosis in renal disease. The nature of the pathologic changes that occur in the kidneys following sulfadiazine therapy would strongly suggest that their superimposition upon those already caused by severe renal disease would aggravate the primary condition and possibly produce or make more serious a uremic condition. A review of the fatal kidney reactions that have been reported in the literature following sulfadiazine therapy[9] and also sulfathiazole and sulfapyridine reveals that in a number of them this was apparently the nature of the death. Our present series includes

none of these cases; the drug has been used in patients with renal insufficiency only when there was great need for it, and at times in reduced dosage as indicated by the blood sulfadiazine levels.

The pH of the urine definitely influences the incidence of renal reactions following sulfadiazine which in most, if not all, cases is due to the precipitation of sulfadiazine compounds in the kidneys and urinary tract. Recently it has been shown[5,6,10] that the solubilities of sulfadiazine and particularly of N_4-acetylsulfadiazine, the compound usually precipitated in the urine, increase markedly with increasing pH within the physiologic pH range of urine. For example, 512 mg. of N_4-acetylsulfadiazine can be dissolved in 100 cc. of buffer solution at pH 7.5 compared with only 18 mg. per 100 cc. at pH 5.[6,7] Furthermore, crystalluria, evidences of renal irritation or of urinary tract obstruction, were not encountered in approximately 200 patients in whom the urine was maintained neutral or alkaline by adjuvant alkali therapy during treatment with 6 gm. daily or more of sulfadiazine orally, or with sodium sulfadiazine intravenously.[7] On the basis of clinical studies, 15.6 gm. daily of sodium bicarbonate (or amounts of other organic sodium salts with equivalent available base excess), divided into 6 doses of 2.6 gm. (40 gr.) administered every 4 hours, is recommended as the dosage usually appropriate to maintain the urine neutral or slightly alkaline during sulfadiazine in adults. We did not observe any gastro-intestinal upsets or other undesirable effects from this dosage of sodium bicarbonate. In the instance of patients suffering from heart failure or impaired renal function, it has been advocated that sodium salts be used cautiously.

We do not consider the maintenance of a large daily volume of urine to be as important a safeguard against the renal reaction as it seems generally to be thought. One-fifth of our 63 patients who had the renal reaction had never had a 24-hour urine volume of less than 1000 cc., and in several the reaction occurred although the output of urine had always been more than 2000 cc. daily. We mention this point chiefly to demonstrate that forcing fluids alone is often insufficient and to emphasize the additional need and efficacy of alkali therapy.

Summary and Conclusions. 1. The toxic reactions that occurred in 1357 hospital patients treated with sulfadiazine orally, or with sodium sulfadiazine intravenously alone or in combination with sulfadiazine orally, are tabulated and analyzed. In this entire group there was 1 fatality, a case of thrombocytopenic purpura which was attributed to sulfadiazine.

2. Eight per cent of 705 patients, who received 6 gm. of sulfadiazine daily for at least 2 days and not more than 14 days, showed evidences of toxicity. The renal reaction was the most frequent single toxic manifestation.

3. With intravenous sodium sulfadiazine the incidence of renal reactions was almost doubled, and thereby the total incidence of reactions was raised.

4. The effect of previous use of sulfonamide therapy upon toxicity was observed in 87 patients, and in these there was a slightly increased

incidence of reactions attributable to a slight increase in drug rash, drug fever, and leukopenia.

5. The renal complications comprised more than half of the toxic reactions following sulfadiazine in the entire series. With the indication that this reaction can be prevented by proper fluid intake, together with appropriate alkali therapy, the total incidence of toxic reactions from sulfadiazine can be reduced to approximately 4%.

6. This study indicates a decided superiority of sulfadiazine over the other commonly employed sulfonamides on the basis of a low degree of clinical toxicity.

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GARGOYLISM

Review of Literature With Report of Two Cases

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In 1936, Ellis, Sheldon and Capon[2] described under the name of "Gargoylism" a syndrome complex which is characterized by chondrodystrophic skeletal changes and deposition of a lipid-like substance in many of the body tissues. The name "Gargoylism" emphasizes the large head, grotesque, inhuman facies, and the deformed limbs which "suggest the appearance of gargoyles," making the patients

look much alike. It has also been referred to as Hurler's Syndrome, Dysostosis Multiplex and Lipochondrodysplasia. Although Hunter, in 1917,[3] was the first to call attention to this condition, Hurler, in 1919,[4] was the first to describe the disease as a separate clinical entity.

In spite of the fact that the disease is easily recognized only a comparatively few cases (50)[1] have so far been reported in the world's literature. This is an indication of its rarity.

The following is a report of 2 cases studied at the Child Guidance Home:

Report of Cases. Case 1. A. B., a white boy, was referred to the Child Guidance Home at the age of 7 years and 8 months for determination of his mental status. According to the mother, the boy had been showing a gradual mental deterioration since the age of 4½ years. She stated that the boy had recited nursery rhymes at the age of 2½ years, articulating well enough to be understood. Two years later, this interest in the rhymes began to wane and his speech became indistinct. It is the mother's feeling that deterioration, as manifested by progressive indifference to mental stimulation, has progressed steadily since that time.

The family history showed that there was no blood relationship between the parents, neither was there a history of epilepsy, mental or nervous diseases, alcoholism, glandular disturbances, feeblemindedness, or of congenital defects in the parents or collaterals.

The patient was the oldest of 2 brothers. He was born to a primipara aged 24. Delivery was instrumental. He weighed 7 pounds and 2 ounces at birth. He was an extremely thin baby. Dentition began at 6 months. He walked at the normal time and began to talk at 1 year. Nutrition, sleep and excretory habits were normal up to that time. He suffered mild attacks of measles, whooping cough and chickenpox in early infancy. At 17 months he was hospitalized because of an increasing deformity of the spine. Roentgenographic examination of the spine at that time revealed an atypical destructive lesion of the 1st and 2d lumbar vertebræ and a diagnosis of spondylitis of unknown origin was made. During his stay at the hospital, it was noted that the boy already had coarse features, thick wrists, large hands, and a very large head. He was examined several months later because of an apparently increasing hydrocephalus. Additional roentgenograms revealed retarded ossification; the spine showed no changes from those previously noted. The sutures of the skull were firmly closed, and the bones of the skull seemed thicker than normal. Except for a marked hearing loss, the other findings were negative.

Physical examination revealed a good nutritional state. The head was large with occipito-parietal flattening; the bossæ were prominent; the face was large and expressionless; the orbits were wide set. There was marked puffiness of the upper eyelids. The nose was saddle-shaped, with wide nares. The lower mandible appeared to be smaller than normal and was misshapen. The lips were thick. The upper teeth were missing, while the lowers were markedly spaced, irregular, peg-shaped, and notched. The general impression was one of grotesqueness and unreality. The boy's posture was also characteristic; he stood with his knees slightly flexed; all the other joints, especially the elbow joints, were also held in a flexed position, giving the child a very awkward appearance. The head was retracted backward and rested on the shoulders, which were slightly rounded. There was a marked thoracolumbar kyphosis and a slight lumbar scoliosis to the right. As a result, the abdomen protruded and resembled a pot belly. The hands were small, but broad, with short tapering fingers. Incurving of all the fingers was also noted.

The boy was 4 inches under height for his age. His weight was normal for his age and height. His measurements were as follows: The circumference of the skull was 21½ inches (55 cm.), bitemporal 13½ inches (34.5 cm.), torso

16½ inches (42 cm.), upper extremities 18 inches (46 cm.), lower extremities 26 inches (66 cm.), vertex to symphysis 21½ inches (55 cm.), symphysis to floor 21½ inches (55 cm.), span 39 inches (99.5 cm.), chest 24 inches (61 cm.), waist 26 inches (66 cm.), and hips 27 inches (69 cm.).

There were no undue deposits of fat, although the boy was rather plump. The skin on the face was rather smooth, while the skin on the rest of the body was dry and rough. The hair on the head was dry and coarse. There was marked hypertrichosis of the extremities and of the back. The thyroid gland was not enlarged.

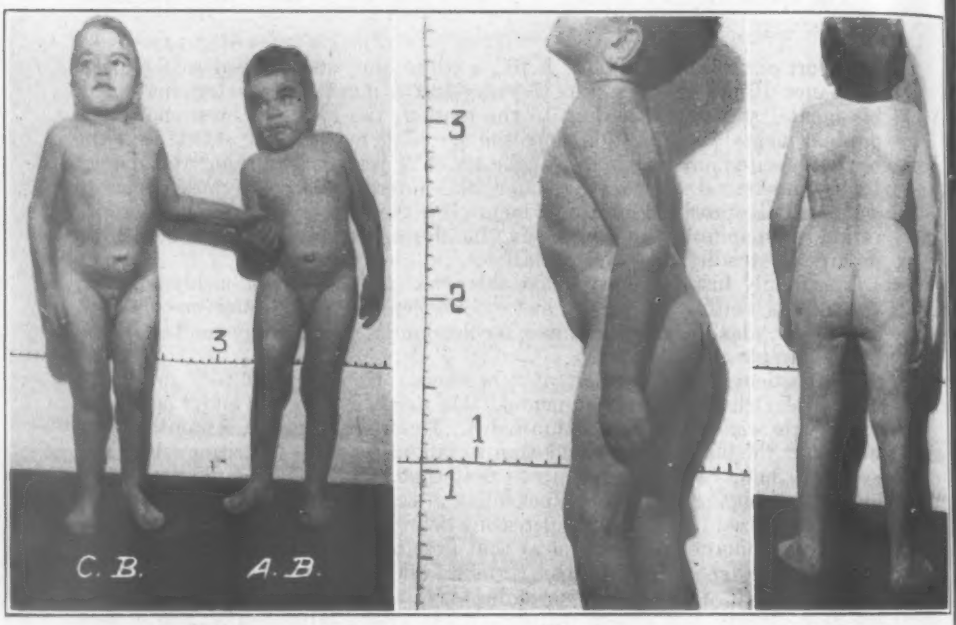

FIG. 1 FIG. 2 FIG. 3

FIG. 1.—C. B. at the age of 6 years 8 months, and A. B. at the age of 7 years 8 months. Note the very typical posture with the retracted head, the short neck, pot belly, tendency to umbilical hernia and the flexed joints.

FIG. 2.—Side view of C. B. at the age of 6 years 8 months. Note the retracted head, the short neck, the rounded shoulders, the thoracolumbar kyphosis, the pot belly, and especially the flexed position of the elbow and knee joints. (Figures on vertical line represent height in feet.)

FIG. 3.—Rear view of A. B. at the age of 7 years 8 months. Note the retracted head, the short neck, the rounded shoulders, the thoracolumbar kyphosis, and the flexed elbow joints. (Figures on vertical line represent height in feet.)

The chest was barrel-shaped. The heart and lungs were negative to percussion and auscultation. There was a marked umbilical hernia, the ring easily admitting 2 fingers. Both the liver and spleen were greatly enlarged. The lower edge of the liver was palpable about 4 finger-widths below the right costal margin. The edge of the spleen was easily palpable just below the level of the umbilicus. The genitalia were small, both testes being in the external rings, which were very large. No secondary sex characteristics were present.

The neurologic examination was negative, except for the absence of the deep tendon reflexes, and the patient's insensitiveness to pain. Bone conduction was normal.

The ophthalmologist reported as follows: "The eye movements were parallel and normal in the cardinal directions. The pupils reacted normally to light, accommodation and consensually. Visual acuity was 20/30 in each eye. The

corneæ, lenses, and mediæ were normal; the fundi were negative; and the intraocular tension was apparently normal."

The otologist reported as follows: "Both drums could not be seen because of cerumen. Bone and air conduction were apparently decreased on both sides. On the audiometric test a hearing loss of over 50% in both ears was noted."

The roentgenographic findings were as follows: "A-P and lateral views of the skull showed an increase in size. The skull was thickened, and the sphenoid bone was unusually large. The sella turcica was larger than normal, but in proportion to the increased size of the skull. The paranasal sinuses were clear. A-P view of the chest showed the great vessels normal in position, shape and size. The heart was somewhat enlarged to both sides. The lung fields were clear. The diaphragm was somewhat elevated. A-P and lateral views of the thoracico-lumbar spine showed a subluxation of the 2d and 5th lumbar vertebræ

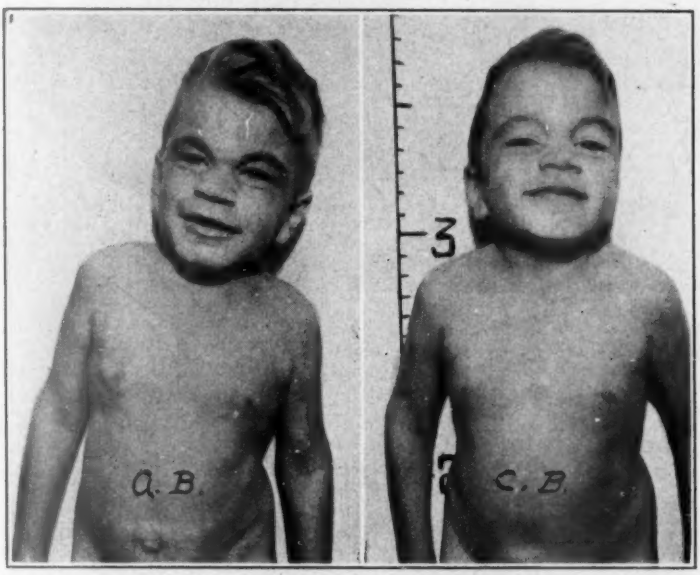

FIG. 4.—Note marked evidence of gargoylism in the two brothers. (Figures on vertical line represent height in feet.)

which were greatly reduced in size. The anterior margins of the bodies of the vertebræ were rounded. The bone age as determined from the ossification centers was 4 years, giving the child a bone quotient of 50.[5] The hands especially showed marked shortening of the bones, which were very broad and thick. There was tufting of the terminal phalanges and marked incurving of the little fingers. All the bones showed poor mineralization." (Figs. 5, 6 and 7.)

The blood count showed 4,560,000 red blood cells, 9300 white cells and 300,960 platelets. Hemoglobin was 13.3 gm. The differential count revealed 38% neutrophils, 49% lymphocytes, 8% monocytes, 4% eosinophils and 1% basophils. There was slight anisocytosis and slight polychromasia. Occasional stippled red cells were seen, and some of the monocytes appeared abnormal.

The blood serologic tests were negative. The sedimentation rate (Cutler) was 24 mm./60 min. The coagulation time was 2 minutes; the bleeding time was 3 minutes. The prothrombin time (Quick) was 23 seconds. Chemical values: fasting blood sugar 76 mg., N.P.N. 27.3 mg., urea N 10 mg., creatinine 1.4 mg., calcium 11 mg., phosphorus 4.5 mg., phosphatase 4.7 units (Bodansky), chloride 607 mg. as NaCl., cholesterol 132 mg., total protein 7.24 mg., albu-

FIG. 5

FIG. 8

FIG. 5. Case 1. (A. B.) Roentgenogram of skull showing flattening of occipital region, prominent frontal bossæ, and slightly enlarged sella turcica. Skull as a whole is enlarged.

FIG. 8.—Case 2. (C. B.) Note the large and thick skull with prominent frontal bossæ.

min 4.64 gm. and globulin 2.6 gm. The blood diastase was 137 units (Somogyi). The direct van den Bergh reaction was negative, while the indirect reaction showed a trace of bilirubin. The icteric index was 10.

The urinalysis was negative. The urine diastase determination showed 20 units of diastase. The hippuric acid liver function test (Quick) showed an output of 2 gm. of benzoic acid in 4 hours.

FIG. 6.—Case 1. (A. B.) Note marked incurving of all the long bones, especially the tibia.

The tuberculin tests, both P.P.D. No. 1 and P.P.D. No. 2, were negative.

Except for sinus arrhythmia, the electrocardiogram was within normal limits.

An attempt was made to obtain an electrō-encephalogram, but because of the patient's uncoöperativeness, this could not be carried out.

On the revised Stanford Binet Test, Form L, the boy made a mental age of 2 years, thus giving him an Intelligence Quotient of 25. He was also tried on the Seguin Form Board, but made no score. On the Vineland Social Maturity Scale, the boy obtained a Social Quotient of 55.4.

The boy's behavior during his stay at the Home was extremely immature and characteristic of a markedly intellectually retarded child. He was very pleasant and coöperative to the best of his ability, which, however, was definitely limited. He was unable to carry out simple directions and needed constant supervision. His speech was guttural, muttered, and indistinct.

His memory for both past ann recent events was very poor. He was dependent on others for his personal needs, being unable to dress or undress him-

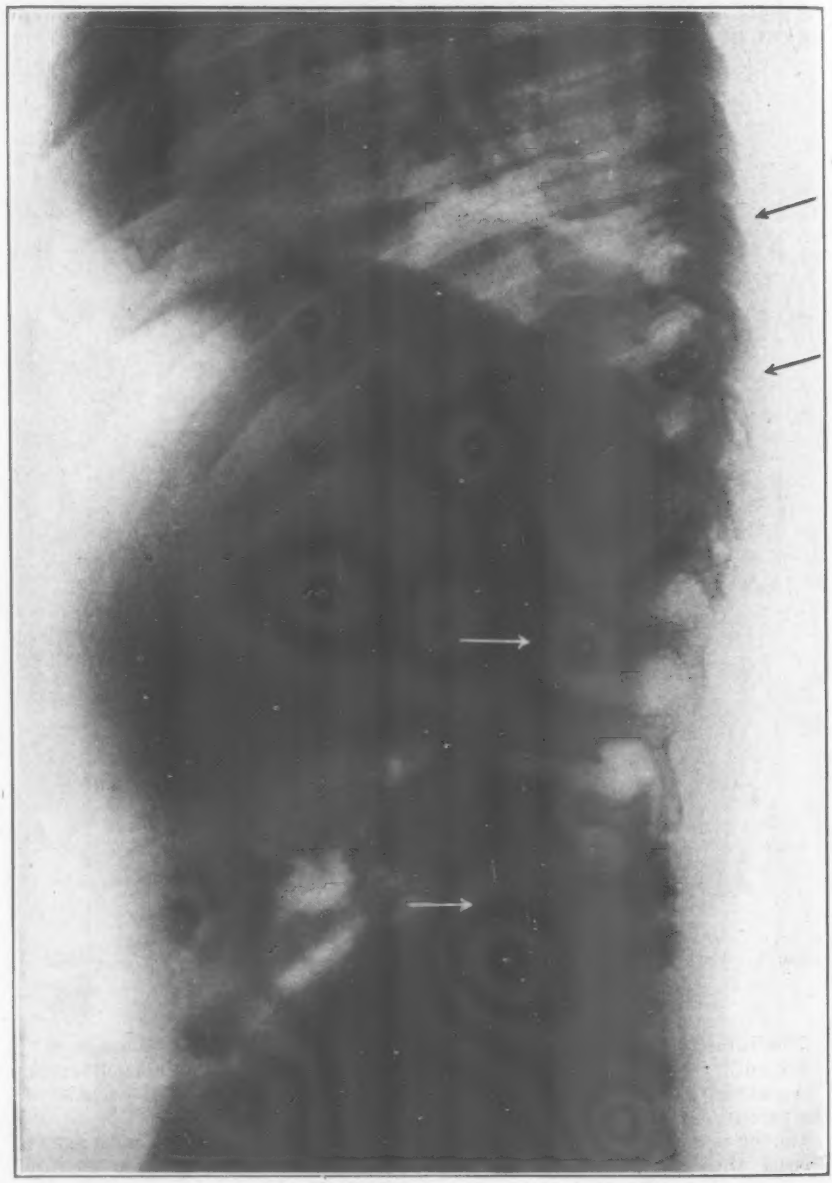

FIG. 7.—Case 1. (A. B.) Note subluxation and reduction in size of 2d and 5th lumbar vertebræ; also the peculiar roundness of the anterior margins of the bodies of all the vertebræ.

self. He could not even feed himself properly. His reactions were entirely those of a feebleminded child, no psychotic manifestations being present.

CASE 2. C. B., a brother of A. B. (Case 1), was 6 years and 9 months old when first seen at Child Guidance Home. Like his older brother, he was referred for determination of his mental status. The boy was attending the first grade in a public school, where he was not making satisfactory progress. The mother also noted that the boy was beginning to present symptoms similar to those of his brother.

The birth and delivery were uneventful. His birth weight was 8 pounds. He teethed at the normal time, began to talk at the age of 1½ years and started to walk when he was about 2 years old. Nutrition, sleep and excretory habits were normal. Like his brother, he suffered from measles, whooping cough and chickenpox during his early infancy. He had never been hospitalized, except for a few days when a tonsillectomy was performed. The mother noted that the boy was subject to colds and upper respiratory infections and that his hearing seemed to be greatly affected when he had a cold.

The boy had identically the same features as his brother. His head was very large with definite occipito-parietal flattening. There was bulging of the forehead with prominent bossæ. The face was large and expressionless. The orbits were widely spaced. A typical saddle-shaped nose and flaring nares were present. The lips were thick, especially the lower. The teeth were widely spaced, and somewhat peg-shaped. The tongue was large, but otherwise normal. His posture was identically the same as that of his brother. He stood with his knees slightly flexed. All the other joints, especially the elbow joints, were also held stiffly flexed, giving the child a very awkward appearance. The head was retracted backward and rested on the shoulders, which were slightly rounded. There was a marked thoracolumbar kyphosis and a slight lumbar scoliosis to the right. As a result, the abdomen protruded and resembled a pot belly. The hands were small, but broad with short tapering fingers. Incurving of all the fingers was present.

He was 2¼ inches under height for his age and 6 pounds overweight for his height and age. The measurements were as follows: The circumference of the skull was 22 inches (56 cm.), bitemporal 14 inches (36 cm.), torso 15 inches (38.5 cm.), upper extremities 18¼ inches (46.5 cm.), lower extremities 26½ inches (67.5 cm.), vertex to symphysis 22 inches (56 cm.), symphysis to floor 21 inches (53.5 cm.), span 43¼ inches (110.5 cm.), chest 25 inches (64 cm.), waist 27 inches (68.5 cm.), and hips 28 inches (71.5 cm.). The boy was plump, but there were no undue deposits of fat. The skin on the face was smooth, while on the rest of the body, it was rough and dry. The hair was dry and coarse. There was marked hirsutism of the extremities and of the back. The thyroid gland was not enlarged.

The chest was barrel-shaped. The heart was not enlarged. However, there was a rough high-pitched systolic murmur, which was heard best in the 3d and 4th intercostal spaces to the left of sternum. The lungs were clear both to percussion and auscultation. The abdomen was protuberant with a large umbilical hernia. The ring easily admitted 2 fingers. Both the liver and the spleen were markedly enlarged. The liver edge was palpable about 2½ finger-widths below the right costal margin, while the edge of the spleen was palpable just below the left costal margin. The genitalia were small. Both testes were still undescended, but could be palpated in the inguinal canals. There was a small left inguinal hernia present. No secondary sex characteristics were present.

The neurologic examination was essentially negative.

The report of the ophthalmologist was as follows: "The eye movements were parallel and normal in the cardinal directions. The pupils reacted normally to light, accommodation and consensually. The visual acuity was 20/30 in each eye. The corneæ, lenses, and mediæ were normal. The fundi were negative. Intraocular tension was apparently normal."

The otologist reported as follows: "Both drums were dull and slightly injected, especially the right. Bone and air conduction were slightly decreased on both sides. There also was an apparent hearing loss in both ears as measured on the audiometer. The exact amount could not be determined."

The roentgenographic findings were as follows: "A-P and lateral views of the skull showed a marked increase in the size of the skull with thickened skull

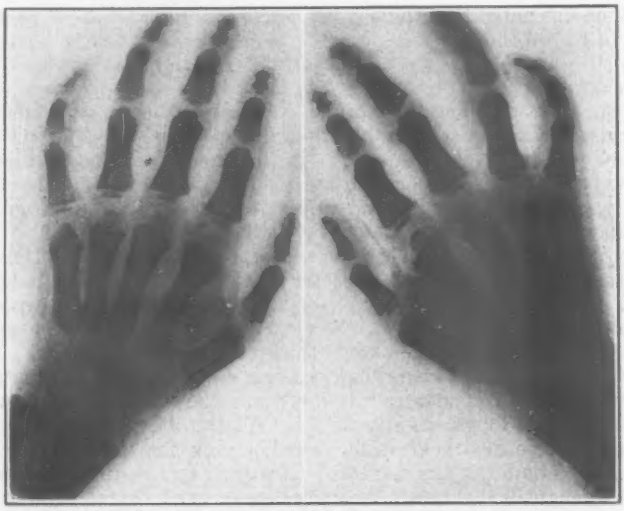

FIG. 9.—Case 2. (C. B.) Note thickened and broadened metacarpals and phalanges with terminal tufting. Also incurving of all fingers. Bone age 3 years.

FIG. 10.—Case 2. (C. B.) Note lack of development of bones of pelvis and lower extremities in contrast to those of upper extremities and skull.

bones. The sutures of the skull were firmly closed. The lower jaw appeared to be out of proportion to the size of the skull. The sella turcica was moder-

ately enlarged but normal in proportion to the increased size of the skull. The paranasal sinuses were clear. Both lung fields were clear. The heart appeared to be slightly enlarged to both sides. The chest as a whole appeared to be very small. The bones of the thoracico-lumbar spine showed roundness of the anterior margins of the bodies of the vertebræ. The pelvic bones and joints were apparently normal. The child's bone age as determined from the ossification centers was 3 years, the bone quotient being 43%.[5] The hands showed shortening of the bones which was very broad and thick. There was marked tufting of the terminal phalanges and marked incurving of the little fingers. The mineralization of all the bones appeared to be poor." (Figs. 8 to 11.)

FIG. 11.—Case 2. (C. B.) Note the peculiar roundness of the anterior margins of the bodies of all the vertebræ.

The blood count showed 4,480,000 R.B.C., 7100 W.B.C., and 318,080 platelets. The hemoglobin was 12.8 gm. The differential blood count showed 48% neutrophils, 31% lymphocytes, 15% monocytes and 6% eosinophils. There was slight polychromasia present and some of the mononuclear cells appeared abnormal. Occasionally stippled red cells were seen.

The blood Wassermann, Kahn, and Kline tests were negative. The blood sedimentation rate (Cutler) was 17 mm./60 minutes. Coagulation time was 2 minutes, while the bleeding time was 3 minutes, 30 seconds. The prothrombin time (Quick) was 22 seconds. Chemical values: fasting blood

sugar 76 mg., N.P.N. 28.8 mg., urea N 9.8 mg., creatinine 1.4 mg., calcium 11.1 mg., phosphorus 4.7 mg. The phosphatase was 4.6 units (Bodansky), chloride 624 mg. as NaCl, cholesterol 123 mg., total protein 7.19 gm., albumin 5 gm. and globulin 2.19 gm. The blood diastase was 82 units (Somogyi). The direct van den Bergh reaction was negative, while indirect reaction showed a trace of bilirubin. The icteric index was 6.

The urinalysis was normal. The urine diastase showed an output of 10 units. The hippuric acid test for liver function (Quick) showed an output of 1.9 gm. of benzoic acid in 4 hours.

The tuberculin tests, both P.P.D. No. 1 and P.P.D. No. 2, were negative.

The electrocardiographic record was within normal limits.

An electro-encephalogram was made. Routine 6 lead bipolar and monopolar tracings were taken. These revealed a somewhat irregular record with, however, a frequency ranging from 6 to 9 per second. Alpha frequencies were best developed in the parietal and the occipital regions. There was no evidence of any focal abnormalities. The record as a whole appeared to be normal.

On the revised Stanford Binet Test, Form L, the boy made a mental age of 3 years, thus giving him an Intelligence Quotient of 44. He was also tested on the Seguin Form Board and the Manikin Test and the results were similar to those made on the Stanford Binet Test. On the Vineland Social Maturity Scale, the boy obtained a Social Quotient of 74.

During his entire stay at the Home the boy was very tractable, but all his reactions were characteristic of a markedly intellectually retarded child. However, he seemed more alert than his brother (Case 1). He was able to carry out his routine duties fairly satisfactorily, although he also needed constant supervision. His memory was poor both for recent and past events. His speech was more intelligible than his brother, although he was able to speak only a few words very plainly. There was no indication of any psychotic behavior.

Discussion. The clinical and laboratory findings as well as the data from the social history permit the diagnosis of Gargoylism in these 2 cases.

Both cases showed the characteristic skeletal deformities, marked enlargement of the spleen and liver, umbilical hernia and feeble-mindedness.

One of the cardinal symptoms, namely, corneal clouding was absent. However, this is not of great significance: Cordes and Hogan[1] have pointed out that corneal clouding is absent in about 25% of the cases. Even when present, it may be very difficult to detect and hence may be overlooked. This is especially true, as in our cases, where slit-lamp examination was not feasible.

Of the laboratory tests, the most significant were those concerned with liver function, all of which gave abnormal values, showing definite liver damage. All the other laboratory examinations including the electro-encephalogram and the electrocardiograms were of interest only from the standpoint of negative findings.

The roentgenograms of the bones showed marked developmental retardation as well as structural changes. The skulls were enlarged but there was nothing characteristic noted about the sella turcica. The shortening and thickening of the bones of the hands as well as the incurving of the fingers were striking.

It has been definitely established that Gargoylism is of congenital origin and familial in nature. It affects both sexes. Consanguinity apparently plays no rôle. Neither are the parents of such children

mentally defective. In our cases, there was no consanguinity, neither were the parents mentally retarded.

From the pathologic-anatomic standpoint, Gargoylism has been placed among the lipoidoses, abnormal storage of lipid-like substances being found in various tissues, principally in the reticulo-endothelial cells, the brain, cornea, pituitary gland, liver, spleen and lymph nodes. The deposits of lipid material appear in the form of fine, curved rod-like granules whose exact chemical nature is as yet undetermined but are said to be probably a complex compound of lipid and protein.

The bony changes, however, cannot be explained on the basis of the lipid disturbance, as Washington[7] has proven. According to him, the enlargement of the skull in these patients is due to a defect in the mesodermal anlage of the top of the skull, while the anomalies in the vertebræ result from stresses on the bodies of the vertebræ whose cartilages have failed to develop. The elongation of the sella turcica as seen in the roentgenograms as well as the depression of the bridge of nose and the widening of the orbits are caused by abnormal development of the sphenoid bone. The disturbance in the epiphyseal growth resulting in dwarfism is probably due to the pituitary involvement. The restricted motion in the finger, wrist and elbow joints is apparently due to poor formation of the articular surfaces.

All the other symptoms, such as the mental retardation, the sexual infantilism, the enlargement of the liver and spleen and the ocular signs are probably caused by the infiltration of the lipid-like substance into these organs.

In regard to the symptomatology, most reports agree that at birth there are usually no abnormalities present. In a few cases, enlargement of the head and some cloudiness of the cornea have been noted at birth. However, in the majority of cases, the first symptoms usually appear between the 1st and 2d year of life when a failure in the normal development of these children is noted. The enlargement of the head and the dorsolumbar kyphosis are usually noted at this time. Growth soon seems to stop and normal physical and mental development ceases altogether, and the child begins to assume the characteristic features which give this condition its name.

This condition must be differentiated from Morquio's disease.[6] The principal differential diagnostic signs are that in the latter condition, there is no limitation of motion of the joints of the body, and the children are not feebleminded.

Summary. Two cases of Gargoylism, occurring in brothers, are reported; and the etiology, clinical and laboratory findings, pathology and differential diagnosis are discussed.

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SURGICAL REMOVAL OF ADRENAL ADENOMA WITH RELIEF OF CUSHING SYNDROME

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In 1941, a 46 year old man entered the Beth Israel Hospital presenting the classical Cushing syndrome. The presence of an adrenal cortical neoplasm was suspected from the pyelographic studies and later confirmed by perirenal insufflation and laminography.[16]

The excretion of androgens in the urine was considerably elevated, whereas the estrogens were within normal limits, suggesting, according to Frank,[8,9] the probability of a benign tumor.

At operation a large encapsulated adenoma of the right adrenal gland was excised and after a stormy postoperative course the patient made a complete recovery. Sixteen months after the operation, he felt well and appeared normal, having lost all the stigmata of his former disease. The postoperative course presented several typical and difficult problems.

Case Report. Beth Israel Hospital No. 137160. A 46 year old man entered the hospital on November 18, 1941, complaining of dizziness and irritability. He was well until 1½ years ago when he noticed blurring of vision of his left eye. At another hospital a diagnosis of diabetes and hypertension was made. On the advice of physicians he submitted to the extraction of his teeth and later to tonsillectomy and vaccine injections. The dizzy spells continued, however, and were associated with headaches, poor memory and irritability. There was no nausea or vomiting. For the past 6 months the patient was sexually impotent.

The patient's general appearance suggested Cushing syndrome (Fig. 1) with marked adiposity of the face, neck and abdomen. The face and neck were dusky red and there were purplish striæ on the abdomen. The testes were small and flabby and the extremities were thin.

The blood pressure was 190 systolic and 118 diastolic. In the next 2 weeks the systolic pressure varied between 190 and 162, and the diastolic between 118 and 106.

Urine examination showed glucose 4+ and albumin, heavy trace. On November 26 and on December 8 the urine again showed glucose 4+, but on December 19 and January 2, it was negative.

Blood glucose on November 19 was 168 mg. and on December 4, 244 mg. Blood non-protein nitrogen on November 19 was 35 mg. Red blood cells were 4,930,000, hemoglobin 100, white blood cells 7600, polymorphonuclears 70%, mononuclears 30%. A Roentgen ray of the skull showed diffuse osteoporosis.

Excretory urography revealed a large circular shadow in the right suprarenal region with downward displacement of the right kidney. The left kidney was normal and the function on both sides was good.

On December 27, 500 cc. of filtered air was injected into the right perirenal space and the simple film and laminogram revealed a large tumor in the right suprarenal region (Figs. 2 and 3).

Androgen determination (17-ketosteroids) of the urine colorimetrically on November 22 showed 92.75 mg. excreted in 24 hours, a marked elevation. Estrogen excretion on November 22 was 110 international units calculated as estrone, or 11 μg. for 24 hours. This is within the normal range.

On a salt-poor diet the patient lost 10 pounds and the blood pressure fell to 152 systolic, 104 diastolic. On November 30, December 1 and 2, 10 cc. of desoxycorticosterone (cortate) was administered.

FIG. 1.—Preoperative photograph showing adiposity of face, neck and abdomen.

Operation. On December 3, 1941, the right kidney and adrenal were exposed through a lumbar incision (S. F. W.). The kidney appeared normal, but directly above it there was an encapsulated tumor mass about the size of an orange. Following resection of the 11th and 12th ribs, the tumor was freed from the posterior parietes and the diaphragm, and delivered into the wound attached only by a narrow vascular pedicle. The pedicle was ligated, doubly clamped and cut, and then again ligated. The kidney was replaced and the wound closed in layers, 1 gauze packing and 1 rubber dam drain coming out of the posterior angle.

Pathologic Report (Drs. A. Plaut and H. Brody). Gross: Irregularly ovoid, moderately soft, tumor mass, 12 x 9.5 x 4.5 cm., weighing 284 gm. (Fig. 4). Except at one pole the tumor appears encapsulated. At this pole it is torn and its original state can no longer be judged. Stretched over one surface, over an area about 4 cm. in length and less than 1 cm. in width, a small fold of normal-appearing suprarenal tissue can be recognized. Through the capsule the tumor appears irregularly lobulated; it varies from yellow-brown to brown; large blood-vessels course beneath the capsule.

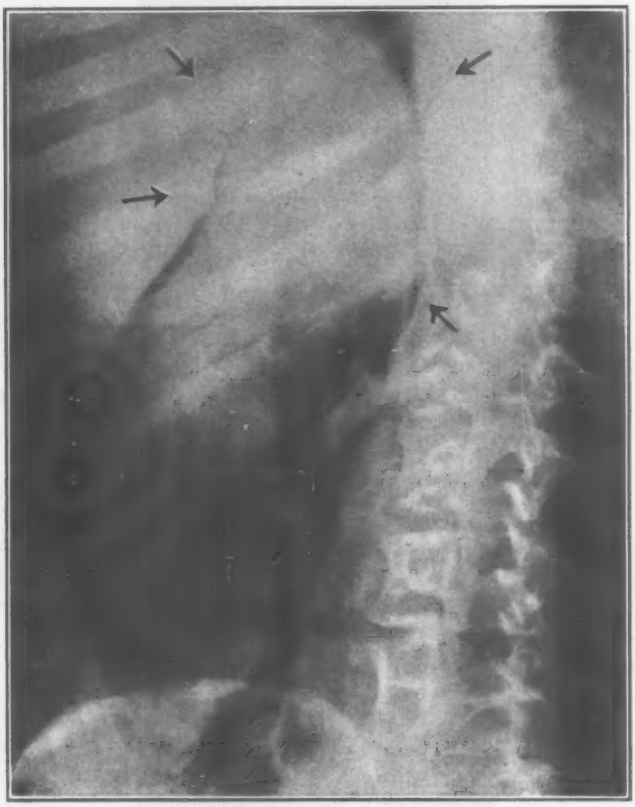

FIG. 2.—Simple film following perirenal insufflation, showing large tumor above right kidney. Oblique view.

On incision, corresponding to the external appearance, a small piece of suprarenal cortex is applied to the tumor. The width of this piece is slightly under 1 cm. On its cut surface two almost paper-thin, closely applied, folded cortical layers can be made out. These layers are very pale yellow, apparently very poor in lipoid. No medullary zone can be recognized. At some levels this portion of adrenal tissue is separated from the underlying tumor by a gray stripe less than 0.5 mm. in thickness, suggestive of connective tissue. It does not have the characteristics of normal medulla.

The tumor has a distinctly lobulated appearance. There is marked variation in the appearance of the different lobules. Perhaps one-third to one-half of the tumor is necrotic, consisting of soft salmon-pink and bloody material. Adjacent to these necrotic portions numerous small thrombosed blood-vessels can be seen. The other nodules for the most part are a dull, light purple-

brown, but yellow areas are scattered about. Some of these have the color which is usually associated with the lipoid in adrenal cortex. Numerous cavities are present, some of which are also lined with similar bright yellow tissue. Some of the areas are peculiarly stippled with yellow and light brown, some areas are more opaque, others more translucent. There are occasional chalky yellow areas, presumably of necrosis. *Sections* were placed in various fixatives, the majority of the tissue being used for chemical analysis.

FIG. 3.—Laminograph delineating tumor of right adrenal gland.

Microscopic. Corresponding to the gross picture, a small cap of suprarenal tissue rides on the large tumor. At a few points a suggestion of zona glomerulosa can be made out. The fasciculata is greatly distorted and its cells are large and fat-laden. The fat is anisotropic. No medullary tissue is found. The central veins are thick-walled. The suprarenal tissue is separated from the tumor by a connective tissue capsule and the suprarenal is stretched and thinned out along the capsule.

The tumor is composed of coarse strands several cells in thickness, separated by a delicate connective tissue network (Fig. 5). In some places the strands broaden to form large sheets of cells. The cells are large and polygonal. The

cytoplasm is for the most part finely granular, although most cells show hyaline eosinophilic areas. The nuclei tend to be centrally located, are fairly regular, though large and occasionally rather bizarrely shaped nuclei are found. The cells contain only occasional sudanophilic granules which are not anisotropic. However, in the areas which were grossly bright yellow, much anisotropic lipoid is present. The tumor contains numerous large vascular spaces with thin walls about which the tumor cells are oriented at right angles.

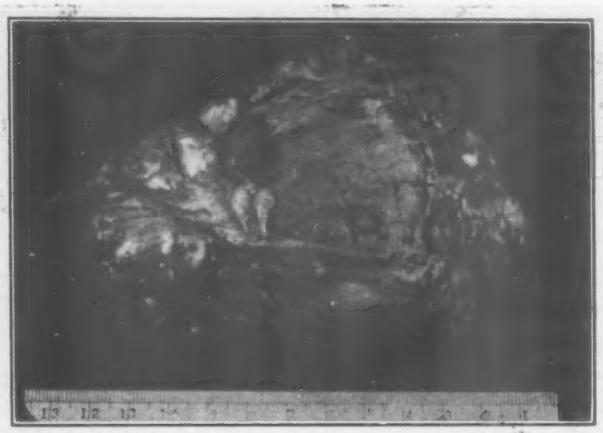

FIG. 4.—Encapsulated adrenal adenoma. Operative specimen.

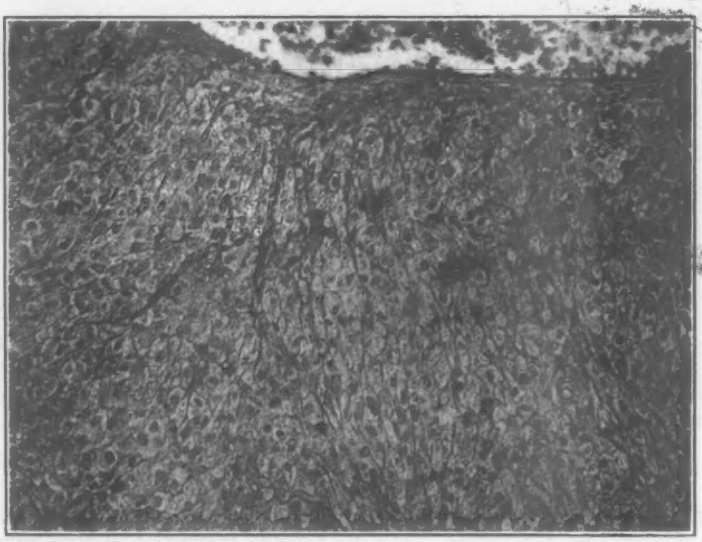

FIG. 5.—Section of adrenal adenoma, × 160.

There are fairly extensive areas of hemorrhage, necrosis and inflammation.

Chemical Analysis (Drs. M. S. Biskind and M. C. Shelesnyak). Part of the tumor was ground and 2 aliquot samples were extracted with carbon tetrachloride, one in the vacuum extractor[14] and the other with the Soxhlet extractor. The phenolic (estrogen) fraction was separated and androgens (17-ketosteroids) were determined colorimetrically. Identical results were

obtained with both extracts: 1.14 mg. androgenic 17-ketosteroids per gram of tissue, or a total of 323.76 mg. for the tumor.

Postoperative Course. The postoperative treatment was directed toward the prevention of adrenal cortical insufficiency. The patient was prepared before operation with the daily administration of 40 mg. of methyl testosterone for 4 days and 10 mg. of cortate daily for 3 days. An hour before operation 1 cc. of cortical adrenal extract (Upjohn) was given intramuscularly.

During the operation a transfusion of 500 cc. of whole blood was given, followed by a continuous intravenous infusion of 0.5% sodium citrate, 1% sodium chloride, and 10% glucose. Frequent blood pressure readings served as a guide for the administration of adrenal cortical extract.

The patient's condition was excellent immediately after operation. The blood pressure was: systolic 160, diastolic 100. The blood pressure level dropped slowly during the day, but the systolic pressure remained above 100 until noon of the next day (December 4). During the first 24 hours after operation, 19 cc. of adrenal cortical extract and 10 mg. of cortate were given in divided doses. In addition, 50 mg. of testosterone were injected.

During the next 24 hours, from noon, December 4, until noon, December 5, the systolic pressure fluctuated between 78 and 108, and the temperature between 102.8° and 104.6° F. The pulse was rapid and irregular, the abdomen distended, and the patient was weak. During these 24 hours, 40 cc. of adrenal cortical extract was administered in divided doses. Normal saline and 5% glucose were given intravenously. Vitamins and calcium gluconate were administered. The urinary output was satisfactory.

During the next 3 days (December 5 to 8) the systolic pressure varied between 120 and 132. Sixty cc. of adrenal cortical extract, 10 mg. of desoxycorticosterone, and 50 mg. of testosterone were given. The patient's condition was good, the temperature remaining at lower levels until December 7, when there was a rise to 103.8° F. with a chill.

On the 5th postoperative day (December 8) the wound was found to be infected. The granulations were pale and in some places necrotic. The wound was opened widely and irrigated with Dakin's solution.

Urinary output was satisfactory until December 10, when the volume of urine was 360 cc. From December 8 to December 10, 35 cc. of adrenal cortical extract was administered, in addition to a large amount of saline solution. The systolic pressure fluctuated between 110 and 136.

On December 10 the patient was very ill, the pulse and respiration were rapid, and the temperature around 103° F. The abdomen was distended and the wound infection was unabated. The extremities became edematous. The blood sodium was 335.8 mg. per 100 cc. and the blood potassium 15.8 mg. per 100 cc.

During the next 24 hours the urinary output was 600 cc. and the edema increased. Ten cc. of adrenal cortical extract had been given but this now was discontinued along with the sodium chloride. Sulfadiazine was administered to combat the resistant wound infection and suspected bronchopneumonia.

On December 12 the wound infection had extended on to the anterior abdominal wall as a brawny cellulitis. This area was widely incised with the evacuation of thin foul pus. The tissues were edematous and in places necrotic. A transfusion of 350 cc. of whole blood was followed by an infusion of 5% glucose in distilled water. The high fever persisted and the patient's condition became steadily worse.

On December 13, the cellulitis had spread and there was visible generalized edema. The urinary output was 460 cc. in 24 hours. At 10.30 A.M., 1.1 cc. of mercupurin and 7.5 gr. of aminophyllin were injected and in the following 48 hours 7660 cc. of urine were voided. That afternoon at the suggestion of Dr. Arthur Fishberg the daily administration of 3 gm. of potassium chloride was begun. Sodium chloride and adrenal extracts were prohibited.

On December 14, the patient appeared better and the systolic pressure remained between 154 and 160. A transfusion of 250 cc. of whole blood was given,

On December 15, the patient's condition had greatly improved, the edema was diminished and the temperature had fallen to 102° F. On the next day potassium and sulfadiazine were discontinued.

For the following 2 weeks the patient improved decidedly and the blood pressure was maintained at levels above 130 systolic and 76 diastolic without adrenal cortical extract or desoxycorticosterone. Androgen determination of the urine on December 22 showed 15.24 mg. for 24 hours, which is within the normal range.

On December 26, the patient began to complain of weakness, persistent nausea and occasional vomiting. The blood sodium was 297.9 mg. per 100 cc. and the blood potassium 22.3 mg. per 100 cc. On December 27 and 28, 5 mg. of desoxycorticosterone were given, and on each of the next 4 days, an average of 5 cc. of adrenal cortical extract. Following ingestion of 1.5 gm. of potassium chloride, the systolic pressure fell to 100.

Ten cc. of adrenal cortical extract were then injected daily until January 9, when the daily dose was increased to 15 cc. On January 2 the urine was negative for glucose and on January 3, 350 cc. of whole blood and an infusion of glucose and saline were given. Despite the nausea and vomiting, the patient improved and sat out of bed on January 9. The temperature then rose to 101.8° F.

On January 12 a slightly tender rounded mass about 6 cm. in diameter was felt in the epigastrium. The mass grew larger and more tender, but, when aspirated on January 14, no pus was obtained. Culture showed *Staph. aureus.*

At operation (S. F. W.) on January 16, a circular fatty tumor 7.5 cm. in diameter was found between the peritoneum and deep rectus fascia. On opening the peritoneum, the mass was seen extending along the falciform ligament with smaller infiltrated fatty nodules in the omentum. The mass was largely but not completely excised and the pathologic report (Dr. A. Plaut) showed inflamed fat tissue.

The patient gradually improved, the wound healing by primary union. The systolic blood pressure fluctuated between 120 and 140 and on January 18, adrenal cortical extract was finally discontinued. Despite a mild phlebitis of the left leg on January 25, the patient was out of bed on February 4. He was much improved and had lost considerable weight. The temperature was normal and the blood pressure was 120 systolic and 92 diastolic. The testicles were firmer and the patient left the hospital on February 8.

Follow-up. On April 8, 1942, the patient was weak but felt well. His physical appearance had changed remarkably. He was thin and looked younger. The red coarseness of the facial skin had disappeared. The blood pressure was 140 systolic, 100 diastolic. The testes were larger and firmer and sexual potency had returned.

On May 25, the patient felt much stronger.

On October 16, the blood pressure was 130 systolic, 90 diastolic. A 24-hour specimen of urine contained 20 mg. of androsterone (non-phenolic 17-ketosteroids).

On December 28, the blood pressure was 120 systolic, and 80 diastolic. Both incisions were firmly healed. The testes were normal and sexual potency continued. The patient felt well but had gained weight by overeating.

On March 13, 1943, the patient said that he was perfectly well, but tired after heavy exertion. The systolic pressure was 128 and the diastolic 85.

Comment. Cushing[6] in 1932 described the now well-known syndrome characterized by plethoric adiposity of the face, neck and trunk, purplish striæ, acrocyanosis, polycythemia and vascular hypertension. This disorder was frequently accompanied by hyperglycemia and osteoporosis, and in women by amenorrhea and hypertrichosis. The finding of a basophilic adenoma of the pituitary at autopsy in 3 of his cases led Cushing to believe that this lesion was the primary cause of the clinical picture. This belief is not commonly accepted.

The association of some of these symptoms with neoplasm of the adrenal gland has been known since 1756 when William Cooke[5] reported his observations on a 7 year old girl who suffered from enormous adiposity and a copious growth of facial and genital hair. Since then many observers, including Apert,[1] Young,[17] Oppenheimer and Silver[13] and others[4,10,15] have reported examples of a clinical picture similar to, or practically identical with Cushing syndrome caused by adrenal cortical neoplasm. Arrhenoblastomata of the ovary and thymic tumors have also been reported with similar clinical features.

Although the first successful operation for adrenal tumor was done in 1889, it is only in the last decade that Broster and Vines,[3] Walters, Wilder and Kepler,[15] Young,[17] Cahill[4] and others[10,12] have reported any considerable number. Most of these occurred in women.

Adrenal operations for classical Cushing syndrome are quite uncommon, and survival following the extirpation of an adrenal neoplasm in these cases is indeed rare. Walters, Wilder and Kepler[15] reported great improvement in a 9 year old girl 6 months after operation. The remainder of their cases, as well as those of Cahill, Oppenheimer and Silver, and others, either died or suffered from adrenal carcinoma. Several patients succumbed shortly after operation in acute adrenal insufficiency. In some of these autopsy revealed atrophy or absence of the contralateral adrenal gland.[2,7] Others progressed favorably for several days but then gradually failed, becoming weaker, and finally succumbing to an intercurrent infection.[13] Such patients apparently suffered from a subacute adrenal insufficiency despite vigorous replacement therapy consisting of adrenal gland extract, desoxycorticosterone, and saline infusions. Atrophy of the contralateral adrenal in these cases is in all likelihood the result of prolonged hypersecretion of adrenal hormones by the neoplasm.

In cases of carcinoma, on the other hand, the danger of postoperative adrenal insufficiency is obviously much reduced by the continued secretion of hormones by neoplastic residua and metastases.

Summary. A 46 year old man presenting a classical Cushing syndrome was found to be suffering from a large adenoma of the right adrenal gland. He was completely relieved of his symptoms following extirpation of the tumor and has remained well for over 16 months after the operation.

Laminography and perirenal insufflation proved valuable in delineating the neoplasm.

The urinary androgens (17-ketosteroids) were greatly elevated. The normal excretion of urinary estrogens suggested the likelihood of a benign neoplasm.

The postoperative treatment was directed toward the prevention of adrenal cortical insufficiency. Frequent blood pressure readings served as an important guide for the administration of adrenal cortical extract, desoxycorticosterone, and saline infusions. On several occasions when the systolic blood pressure fell below 100, adrenal cortical extract (Upjohn) was administered intravenously with gratifying results. The efficacy of intravenous adrenal cortical extract precludes the necessity for prolonged preoperative preparation.

The danger of overtreatment with adrenal cortical extract, desoxycorticosterone, and saline infusion was vividly illustrated from the 7th to the 12th postoperative day. Oliguria and severe anasarca were successfully combated by the discontinuance of adrenal cortical extract, desoxycorticosterone, and sodium chloride, and by the prompt administration of mercupurin, potassium chloride, and 5% glucose in distilled water.

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HEART DISEASE IN SELECTIVE SERVICE EXAMINEES

A Study of 20,000 Examinees in the Pacific Northwest*

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Heart disease occupies a major place among the nation's health problems, and is at present responsible for an appreciable percentage of rejections from military service. This study was undertaken to determine the types and frequency of heart disease among 20,000 consecutive Selective Service examinees appearing before the Army Examining Board at this station. No such survey has appeared thus far.

Rowntree, McGill and Folk[6] in a statistical survey of the physical and mental causes for rejection in 18 to 36 year old examinees, reported cardiovascular defects to be responsible for an estimated 10.6% of

* At the time this study was conducted the Station was situated in Tacoma, Wash., functioning as the U. S. Army Examining and Induction Station.

total rejections. More recently, in a similar survey in Tennessee, Fenn and his associates[3] reported rejections for cardiovascular defects as 4.4% of the men examined. However, it should be noted that these figures include, in addition to heart disease, the various other cardiovascular causes for rejection such as hypertension without cardiac disease, peripheral vascular disease, persistent tachycardia, and (in Rowntree, McGill and Folk's study) varicose veins. McKinlay[4] reported heart disease as responsible for 10.5% of 209 Selective Service examinees rejected by local board examiners in Minnesota for defects within the field of internal medicine.

Our study is based on the examinations of 20,000 consecutive Selective Service examinees, ranging in age from 20 to 45 years, and representing a cross-section male population of corresponding age in the western half of the state of Washington.* These include urban and rural inhabitants: Professional men, white collar workers, skilled and unskilled laborers, and farmers. The vast majority is of the white race. A small percentage (less than 3%) include the Indian, negro, Chinese, and Filipino races, of which the Indian is the most common.

Diagnosis was based upon the criteria adopted by the American Heart Association,[5] and recommended by the War Department,[7] and was established by history, physical examination, exercise tolerance, stereoroentgenograms,† and when indicated, electrocardiograms.

TABLE 1.—TYPES AND FREQUENCY OF HEART DISEASE ENCOUNTERED IN 20,000 EXAMINEES

Type of heart disease	No. of cases	Total cardiac rejections (%)	Rejections per 1000 examinees
Rheumatic	183	63.5	9.15
Congenital	35	12.2	1.75
Arteriosclerotic	9	3.1	0.45
Hypertensive	6	2.1	0.30
Hyperthyroid	3	1.0	0.15
Effort syndrome (neurocirculatory asthenia)	3	1.0	0.15
Paroxysmal tachycardia	2	0.7	0.10
Chronic constrictive pericarditis	1	0.3	0.05
Organic disease of unknown etiology	46	16.0	2.30
Total	288	99.9	14.40

TABLE 2.—REJECTIONS FOR HEART DISEASE AS COMPARED TO REJECTIONS FOR ALL PHYSICAL AND MENTAL DEFECTS IN THE 20,000 MEN EXAMINED

Cause for rejection	No. of rejections	Total examinees (%)	Relative‡ percentage
Heart disease	288	1.44	6.0
All physical and mental defects	4820	24.10	100.0

Incidence and Types of Heart Disease. Heart disease was observed in 288 of the 20,000 men examined, an incidence of 1.44%, or 14.4 cardiac rejections per 1000 men examined. Rejections for cardiac

* All Army induction examinations for the western half of the state of Washington are conducted at this Station.

† Stereoroentgenograms were 4 x 5 inches in size, and taken at a target-film distance of 42 inches. Proper consideration was given this factor.

‡ Percentage cardiac rejections as compared to total physical and mental rejections.

disease constituted 6% of total rejections for physical and mental defects (Table 2). Table 1 summarizes the various types and frequency of cardiac disease encountered. Rheumatic heart disease was the most common, occurring in 183 examinees, or 63.5% of total rejections for heart disease and 9.15 men per 1000 examined. Congenital heart disease was observed in 35 instances, or 12.2% of cardiac rejections and 1.75 men per 1000 examinees. Arteriosclerotic heart disease was observed in 9 instances or 3.1% of heart disease encountered, and 0.45 men per 1000 examined; in this group were 3 cases of myocardial infarction (all less than 1 year old), and 1 man exhibiting a well-defined anginal syndrome. Six cases (2.1% of rejections for heart disease; 0.3 men per 1000 examined) of hypertensive heart disease were present; these do not include examinees rejected for hypertension without cardiac disease. Three cases (1% of cardiac rejections; 0.15 men per 1000 examined) of hyperthyroid heart disease were noted and were confirmed by high basal metabolic rates. Unequivocal effort syndrome (neurocirculatory asthenia) was encountered in only 3 instances (1% of cardiac rejections; 0.15 per 1000 men) in our series. Two examinees (0.7% of cardiac rejections; 0.1 men per 1000) were rejected for paroxysmal tachycardia.* One case (0.3% of cardiac rejections; 0.05 men per 1000 examined) of chronic constrictive pericarditis was noted. Forty-six cases (16% of cardiac rejections; 2.3 men per 1000 examined) of organic heart disease of undetermined etiology were encountered in our series.

Table 3 represents the relative frequency of the various types of valvular involvement found in those men rejected for rheumatic heart disease. No examinee was rejected merely on the basis of a history

TABLE 3.—VALVULAR DEFECTS IN EXAMINEES REJECTED FOR RHEUMATIC HEART DISEASE

Valvular defect	No. of cases	Per cent
Mitral	**152**	83.1
Insufficiency	92	50.3
Stenosis	22	12.0
Stenosis and insufficiency	38	20.8
Aortic	**8**	4.4
Insufficiency	4	2.2
Stenosis	1	0.5
Stenosis and insufficiency	3	1.6
Combined mitral and aortic	**23**	12.5
Total	183	100.0

of rheumatic fever. The mitral valve was involved alone in 152 (83.1%) of the 183 cases, mitral insufficiency occurring in 92 men (50.3%), mitral stenosis in 22 (12%), and mitral stenosis and insufficiency in 38 (20.8%). The aortic valve was involved alone in only 8 examinees (4.4%); in these, aortic insufficiency was noted in 4 men (2.2%), aortic stenosis in 1 examinee (0.5%), and aortic stenosis and insufficiency in 3 examinees (1.6%). Combined mitral and aortic

* Examinees subject to attacks of paroxysmal tachycardia are not acceptable for military service (War Dept., Mobiliz. Reg. No. 1–9, Sect. XIV, Par. 64d, March 15, 1942).

lesions were present in 23 men (12.5%). In the last group, although specific diagnoses of the character of valvular involvement were included in our examination records, we are omitting these in this report because of the significant percentage of error undoubtedly associated with such attempted accuracy.

The predominant congenital anomalies observed in the men rejected for congenital heart disease are summarized in Table 4. Interventricular septal defect was the most frequent anomaly noted, occurring in

TABLE 4.—PREDOMINANT CARDIAC DEFECTS IN EXAMINEES REJECTED FOR CONGENITAL HEART DISEASE

Predominant cardiac defect	No. of cases
Interventricular septal defect	11
Patent ductus arteriosus	5
Interventricular septal defect with congenital A–V block	1
Interauricular septal defect	1
Coarctation of the aorta	1
Pulmonary stenosis	1
Undetermined types	15
Total	35

11 examinees. Patent ductus arteriosus was observed in 5 men. One instance of interventricular septal defect and congenital complete auriculoventricular block was encountered in a 39 year old man. One case each of interauricular septal defect, coarctation of the aorta and pulmonary stenosis were present, the last associated with moderate cyanosis and marked clubbing of the fingers. There were 15 cases of congenital heart disease of undetermined type.

Early to moderate congestive heart failure was observed in 5 instances, occurring in 2 examinees with rheumatic heart disease and mitral stenosis (1 of which also exhibited auricular fibrillation), in 1 examinee with congenital heart disease, in 1 with hypertensive heart disease, and in 1 with organic heart disease of unknown etiology. Two cases of auricular fibrillation were encountered, both occurring in examinees over the age of 40, with rheumatic heart disease and mitral stenosis.

TABLE 5.—COMPARISON BETWEEN INCIDENCE OF HEART DISEASE AND FUNCTIONAL MURMURS

	No. of cases	Total examinees (%)
Heart disease	288	1.44
Functional murmurs	297	1.48

It might be of interest to comment briefly on several non-disqualifying cardiac conditions encountered in the 20,000 men examined. Among these were 2 instances of congenital dextrocardia, and 1 man with a previous bullet wound of the heart, the bullet having been surgically excised, with subsequent cardiac function remaining unimpaired. Functional murmurs were noted in 297 (1.48%) of the 20,000 men examined, an incidence slightly higher than that observed for all forms of cardiac disease combined (Table 5). The occurrence of premature systoles was relatively infrequent, and may be due, as sug-

gested by White,[8] to the cardiac acceleration resulting from the nervous tension and excitement associated with the induction examination. The majority of the examinees exhibited heart rates between 85 and 100.

Comment. It is intended that this report be as brief as possible. However, several recent studies warrant mention despite the fact that the ages represented are not strictly comparable. Cole,[1] in a survey of the incidence of heart disease among 28,139 students at the University of Wisconsin, observed organic heart disease in 1.02% of the students, with a sex relationship of 1.7 females to 1 male. Cuykendall[2] observed an incidence of 1.1 (54 cases) of 4991 male students at Cornell University. Rheumatic heart disease comprised 0.8%, and congenital heart disease 0.26% of this number; in addition 1 case of subacute bacterial endocarditis was encountered.

The absence of syphilitic heart disease in our series warrants comment. It is apparently the result of 3 important factors: (1) examinees with positive serologic reactions for syphilis were disqualified from appearing before the Army Examining Board; (2) the low incidence of negro examinees at this station; and (3) the relatively small percentage of examinees over the age of 40 (approximately 9%). In view of the last, it is probable that the incidence of syphilitic heart disease would have been low regardless of the preceding two factors, and consequently would not have significantly influenced the number of rejections for heart disease.

Summary. 1. A study of 20,000 consecutive Selective Service examinees, representing a cross-section of male population 20 to 45 years of age in the Pacific Northwest, revealed the existence of heart disease in 288 men, an incidence of 1.44%. This figure constituted 6% of rejections for all physical and mental defects.

2. Rheumatic heart disease was observed in 183 examinees, or 63.5% of cardiac rejections and 9.15 men per 1000 examined. Congenital heart disease followed in frequency, occurring in 35 men (12.2% of rejections for heart disease, or 1.75 men per 1000 examined). There were 9 instances of arteriosclerotic heart disease, 6 examinees with hypertensive heart disease, 3 cases each of hyperthyroid heart disease and effort syndrome (neurocirculatory asthenia), 2 instances of paroxysmal tachycardia, and 1 case of chronic constrictive pericarditis.

3. There were 46 cases of organic heart disease of unknown etiology, or 16% of total cardiac rejections and 2.3 men per 1000 examined.

4. In the 183 examinees rejected for rheumatic heart disease the mitral valve was involved alone in 152 cases (83.1%), the aortic valve was involved alone in 8 examinees (4.4%), and combined mitral and aortic valve defects were observed in 23 cases (12.5%).

5. Functional murmurs were noted in 297 examinees, an incidence of 1.48% of the total number of men examined. This figure represents an incidence slightly higher than that observed for all forms of cardiac disease combined.

6. The figure of 288 men rejected for heart disease (1.44% of 20,000 examinees) is of interest in comparison with the 4820 rejected for all physical and mental defects (24.1% of examinees). (See Table 2.)

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A CLINICAL AND BIOCHEMICAL STUDY OF COW'S MILK AND HONEY AS AN ESSENTIALLY EXCLUSIVE DIET FOR ADULT HUMANS*

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The nutritional deficiencies of cow's milk for adults are at present recognized as consisting largely of inadequate concentrations of iron, copper and manganese and frequently iodine, and a low caloric value in proportion to its bulk. The ascorbic acid content of most pasteurized milk is also inadequate. Although the thiamine content is actually quite low because of the high water content, it is adequate in relation to its caloric value. According to Melnick,[25] the thiamine requirement of adult humans is 350 micrograms per 1000 Calories. Whole cow's milk having 3.5% fat contains, on the average, 750 micrograms of thiamine per 1000 Calories. The surprisingly low nicotinic acid content of cow's milk has not been yet reconciled with its established antipellagra value. The importance for adults of the normally low vitamin D has not been determined.

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There have been very few experimental studies in which milk was the major article of diet for adults for a considerable period of time. Neff[31] described an experiment in which 9 men limited their diet for 1 month to plain milk or gelatinized milk, with a supplement of 1 or 2 oranges daily. All the subjects continued their regular laboratory work without interruption and apparently remained in excellent health. Irwin,[21] describing the beneficial effects of milk as a dietary adjunct, states, that "For 3 months one winter several men students lived on raw milk supplemented with the missing minerals and with orange juice. They drank as much as they wanted—usually 3½ to 4½ quarts a day. They maintained their weight, in fact some of the boys gained, and they all felt well and satisfied." This experiment apparently has not been published in detail.

Experimental animals have been employed for studies on the effect of extended feeding of liquid cow's milk fortified with minerals or calorigenic substances. Daniels and Hutton[11] reported the successful rearing of 5 generations of rats on boiled milk after addition of only iron, iodine, aluminum, fluorine, manganese and silicon salts. Daniels and Everson[10] found that a boiled milk-iron-copper diet sufficed for 4 generations but that manganese was necessary for a 5th generation. Kemmerer *et al.*[23] secured as good growth and development of rats and pigs on cow's milk supplemented with iron, copper and manganese as with a stock ration. Anderson *et al.*[1] found that a supplement of iron, copper, manganese and cod-liver oil to raw cow's milk made it adequate for 2 generations of dogs, and maintained male dogs in normal health for 3 years.

Van Donk and co-workers[49] found that the addition of sucrose to mineralized cow's milk improved its value for growth, ovulation and reproduction of rats. The comparative chemical composition of milk and honey (average analyses) shows that dark honey is 4.6 times richer in caloric value, 5.3 times richer in iron, 100 times richer in manganese and 7.3 times richer in copper than cow's milk which would seem to make it an ideal supplement so far as its energy and mineral deficiencies are concerned. Light honey is poorer in these mineral constituents (Table 1). Haydak, Palmer and Tanquary[17] have shown that a cow's milk-dark honey diet will both cure and prevent nutritional anemia in rats.

Haydak[16] subsisted for 3 months on a cow's milk-honey mixture consisting of 100 gm. of honey per quart of milk. He found that his ability to work was normal and that no sluggish or tired feeling developed. The clinical observations were limited but showed no loss of weight, normal bowel movements, absence of proteinuria and glycosuria and slight rise in hemoglobin content of the blood. However, toward the end of the experiment, certain symptoms suggestive of vitamin C deficiency were noticed, consisting of fresh blood in the feces, dryness of the skin, a hyperemic area on the gums, numbness and ulceration of the tongue and small reddish papulæ on the forehead and face. All these symptoms were promptly cured by orange juice.

The present study was prompted by a desire to conduct a more

extensive investigation of the type carried on by Haydak, involving a larger number of subjects, a much more complete biochemical analysis of the blood and urine as well as a more comprehensive clinical and dental study.

TABLE 1.—COMPOSITION OF MILK AND HONEY. AMOUNTS PER 100 CC. OR GM.

	Milk	Honey	
		Light	Dark
Calories	69	320	320
Protein, gm.	3.5		
Ca, mg.	120		
P, mg.	93		
Cu, mg.	.015	.030*	.11*
Fe, mg.	.24	.24*	1.28*
Mg, mg.	12		
Mn, mg.	.004	.03†	.41†
Thiamine, μg.	50	5.5	5.5
Riboflavin, μg.	190	61	61
Ascorbic acid, mg.	2	2.4	2.4
Nicotinic acid, mg.	.21	.36	.36
Pantothenic acid, μg.	.40	.10	.10

* Haydak, Palmer, Tanquary.[17]
† Schuette and Remy.[39]

Diet and Methods. Five healthy individuals (4 males and 1 female) varying in age from 22 to 44 years were put on the diet consisting of a mixture of 1 quart of pasteurized milk with 100 gm. of light honey. The University creamery supplied the milk. A mixed honey (from sweet and white clover) from the University apiary was used throughout the experiment. The diet was carefully prepared daily, bottled and distributed to all the experimental subjects.

Because pasteurized milk is low in ascorbic acid and is only a moderately good source of thiamine, a solution containing 65 mg. ascorbic acid and 1 mg. thiamine chloride was added daily to the diet of each individual as well as 1 drop of 10% solution of KI. There were 2 control and 2 test periods for each subject. These were alternated and lasted for about 4 weeks. During the control periods the subjects ate their normal customary diet. No attempt has been made to record the diet during the control periods. There was a 3-day transition before the first test period but for the second test period this was abolished.

All the participants started the milk and honey diet simultaneously. They kept a complete record of the amount of the mixture consumed. The number and the character of stools was also recorded daily as well as the general subjective feeling of each subject.

At the end of each control and test period a thorough physical and dental examination was made, 50 cc. of blood and 24-hour urine samples taken for further study and a capillary fragility test performed. Blood and urine samples were also taken at the middle of each test period. The blood samples were taken before breakfast. The urine samples were kept in a refrigerator during collection and until analyzed.

About the second day of the test period the tongues of all the subjects became coated with a white film and that phenomenon lasted through-

out each test period. As a rule, the bowel movements were normal in all the participants. The feces were light yellow in color and of soft consistency. One subject (W. N.) had occasional difficulty in defecation due to the hardness of the stools. One (E. V.) had diarrhea, of a day's duration 4 times during the first period. Twitching of the eyelid was experienced by some individuals toward the end of the test diet, but this was also observed during the control period. One (W. N.) felt cramps in the stomach several times during the first week of the first test period. Four days before the end of the first test period one of the individuals (R. R.) became ill (common cold). At the middle of the second control period another (E. V.) contracted virus pneumonia. Neither of these subjects participated in the second test period.

Food Consumption. On the basis of data presented in the literature Table 1 was constructed, showing composition of the milk and honey for use in computing the consumption of the various food components in which we were interested. The data for the vitamin contents of the honey were taken from the corrected paper by Haydak and coworkers,[18] the original values for the nicotinic acid being divided by 100.

According to the Committee on Food and Nutrition of the National Research Council, the following minimum daily requirements are suggested for adult humans: protein, 70 gm.; Calories, 3000; Ca, 800 mg.; Fe, 12 mg.; vitamin A, 5000 I. U.; thiamine, 1.8 mg.; riboflavin, 2.7 mg.; ascorbic acid, 75 mg.; nicotinic acid, 18 mg.

Table 2 gives the average daily consumption for each individual as well as the consumption of various essential dietary components. It shows that except for nicotinic acid and iron the subjects in the first experimental period ingested more than the minimum daily requirement of all the dietary units for which acceptable standards have been proposed. The iron intake, especially that of AB, was considerably below the normal requirement in both periods. A submaintenance Caloric intake was one of the causes of this inadequacy and was accompanied by a loss of weight.

Results of Blood and Urine Analysis. Determinations were made of the calcium, phosphorus, magnesium, ascorbic acid and pantothenic acid contents of the blood plasma. The thiamine, riboflavin and nicotinic acid contents of whole blood were also determined.

For the urine determinations, aliquots from the 24-hour samples were taken. The methods used were: for calcium, Clark and Collip[9] modification of Kramer and Tisdall procedure; for phosphorus, that of Fiske and Subbarow;[13] for magnesium, that of Briggs;[7] for thiamine, that of Hennessy and Cerecedo;[19] for riboflavin, that of Snell and Strong;[42] for ascorbic acid, Bessey;[5] for pantothenic acid, Strong, Feeney and Earle;[46] for nicotinic acid, Snell and Wright.[43]

Table 3 shows that the calicum, magnesium and inorganic P contents of blood plasma were within the limits of normal variation, although the inorganic P tended to be on the lower side of the normal range. However, there is no evidence that this was related to the special diet employed. Robertson[36] gives the variations in Ca and inorganic P content of plasma for 60 normal adults between 20 to 40 years of age

TABLE 2.—AVERAGE FOOD CONSUMPTION PER DAY

Name	Sex	Age	Weight, initial and final (lbs.)	Mixture (cc.)	Milk (cc.)	Honey (gm.)	Protein (gm.)	Calories	Ca (gm.)	P (gm.)	Mg (gm.)	Fe (mg.)	Cu (mg.)	Mn (mg.)	Thiamine* (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)	Nicotinic acid (mg.)	Pantothenic acid (mg.)	Thiamine per 1000 Cal. (μg.)
First Period: March 1, 1942–March 29, 1942																				
A. B.	F	22	143–138	1900	1769	187	62	1819	2.1	1.6	.2	4.7	.3	.1	1.9	3.5	104.9†	4.4	7.3	1045
M. H.	M	44	145–140	3230	3008	317	105	3090	3.6	2.8	.4	8.0	.6	.2	2.5	5.9	132.7†	7.5	12.4	809
W. N.	M	38	142–150	4275	3982	419	139	4089	4.8	3.7	.5	10.6	.7	.3	3.0	7.8	154.7†	9.6	16.4	734
R. R.	M	25	135–140	4370	4070	428	142	4178	4.9	3.8	.5	10.8	.7	.3	3.1	8.0	156.7†	10.0	16.7	742
E. V.	M	26	134–123	2755	2566	270	90	2534	3.1	2.4	.3	6.8	.5	.2	2.3	5.0	122.8†	6.4	10.5	908
Second Period: May 4, 1942–May 27, 1942																				
A. B.	—	—	139–139	1900	1769	187	62	1819	2.1	1.6	.2	4.7	.3	.1	1.9	3.5	169.9‡	4.4	7.3	1045
M. H.	—	—	145–145	3610	3361	354	118	3453	4.0	3.1	.4	8.9	.6	.2	2.7	6.6	234.9‡	8.3	13.8	782
W. N.	—	—	153–158	3990	3716	391	130	3815	4.5	3.5	.4	9.9	.7	.3	2.9	7.3	213.7‡	9.1	15.3	760

* A supplement of 1 mg. of thiamine chloride is included.
† Of this number 65 mg. were added as synthetic ascorbic acid.
‡ Of this number 130 mg. were added as synthetic ascorbic acid (from May 4 to May 19).
§ Of this number 195 mg. were added as synthetic ascorbic acid (from May 20 to May 27).

TABLE 3.—BLOOD AND URINE ANALYSES

Name	Sex	Age	Blood analysis (μg., mg. and gm. per 100 cc.)										24 hours urinary excretion							Misc.
			Hb (%)	Hema-tocrit	Total protein plasma (gm.)	Ca plasma (mg.)	P (inorg.) plasma (mg.)	Mg plasma (mg.)	Thia-mine whole blood (μg.)	Ribo-flavin whole blood (μg.)	Ascorbic acid plasma (mg.)	Pant. acid plasma (μg.)	Nicot. acid whole blood (mg.)	Vol-ume (cc.)	Spec. gravity	Thia-mine (μg.)	Ribo-flavin (μg.)	Ascorbic acid (mg.)	Pant. acid (mg.)	Nicot. acid (mg.)	Pete-chiæ count (No.)
End of Normal Diet Feb. 18, 1942																				
A. B.	F	22	99	..	..	9.6	3.3	..	6.5	..	.2	..	..	1000	1010	41.3	..	31.6			
M. H.	M	44	86	..	..	9.1	3.2	..	5.1	..	.3	..	..	1650	1020	49.2	..	20.1			
W. N.	M	38	92	..	..	10.0	3.8	..	7.2	..	.4	..	..	1130	1025	50.1	..	40.6			
R. R.	M	25	78	..	..	10.9	2.9	..	9.2	..	.3	..	..	1825	1015	46.4	..	36.7			
E. V.	M	26	93	..	..	10.2	4.0	..	5.3	..	.7	..	..	1000	1025	51.2	..	19.4			
Honey Diet. Middle of the First Period, March 16, 1942																				
A. B.	.	.	96	..	..	9.9	3.2	..	6.7	..	.2	..	..	860	1005	40.2	..	30.2			
M. H.	.	.	95	..	..	9.6	3.2	..	5.3	..	.3	..	..	2070	1010	46.1	..	15.6			
W. N.	.	.	92	..	..	10.3	3.8	..	7.8	..	.5	..	..	2700	1005	56.3	..	35.2			
R. R.	.	.	..	..	..	10.9	2.6	..	10.4	..	.4	..	..	2820	1010	40.1	..	30.1			
E. V.	.	.	95	..	..	10.6	4.0	..	5.1	..	.8	..	..	480	1025	59.6	..	20.9			
Honey Diet. End of First Period, March 30, 1942																				
A. B.	.	.	98	47.5	7.9	9.9	3.2	1.5	6.8	50	1.4	16.3	..	840	1010	40.6	521.7	30.1	3.4	2.7	57
M. H.	.	.	98.5	48.8	7.0	10.0	3.0	2.2	6.4	80	.8	6.3	..	1200	1015	40.3	401.1	15.4	2.4	3.4	0
W. N.	.	.	106	50.5	7.0	10.8	3.8	2.1	7.8	50	1.5	10.4	..	2880	1005	57.9	623.2	35.0	3.9	5.5	33
R. R.	.	.	87	..	..	11.2	3.3	1.6	9.4	40	..	8.7	..	480	1015	53.1	470.3	30.0	1.9	3.2	
E. V.	.	.	106	50.8	8.4	10.9	3.7	1.8	5.4	40	1.0	7.4	..	1100	1015	60.3	423.1	18.6	1.9	5.1	4
End of Normal Diet, April 30, 1942																				
A. B.	.	.	90	42.0	7.8	9.3	3.3	1.6	6.4	40	.3	16.0	.2	820	1005	..	990	35.3	3.8	..	23
M. H.	.	.	91	45.1	7.7	9.0	3.4	2.1	6.2	60	1.0	6.1	.3	880	1025	..	1554	19.3	2.2	..	0
W. N.	.	.	96.5	47.2	7.9	10.2	3.8	2.1	7.6	40	.3	10.9	.5	1175	1015	..	470	41.6	4.0	..	7
Honey Diet. Middle of the Second Period, May 20, 1942																				
A. B.	.	.	88	..	..	9.9	3.0	1.7	6.8	50	.3	14.3	.4	860	1005	40.1	517	31.7	3.4	2.3	14*
M. H.	.	.	91	..	..	9.8	3.0	2.2	6.9	60	.4	6.0	.3	2420	1010	47.3	462	17.6	2.1	2.7	1
W. N.	.	.	97	..	..	10.9	3.4	2.0	8.3	40	.5	10.6	.5	2410	1015	56.4	633	40.0	3.7	5.8	2*
Honey Diet. End of the Second Period, May 27, 1942																				
A. B.	.	.	83	41.8	7.0	10.1	3.0	1.7	6.2	60	.3	14.4	.3	560	1005	39.3	530.7	32.6	3.6	3.0	2†
M. H.	.	.	95	47.3	7.1	9.8	3.0	2.3	7.3	70	.4	6.4	.3	2700	1005	51.2	470.1	16.2	2.2	2.8	0
W. N.	.	.	97	48.0	6.8	10.9	3.6	2.0	8.3	50	.6	10.1	.5	2280	1010	54.6	620.6	39.3	4.0	5.1	0

* 130 mg. synthetic ascorbic acid was added to the diet.
† 195 mg. synthetic ascorbic acid was added to the diet.

as 9.9 to 11.1 mg./100 cc. and 3.1 to 4.8 mg./100 cc., respectively. Hirschfelder[20] considered the normal variation for the plasma Mg. to be from 1.8 to 2.5 mg./100 cc.

From the table it is also evident that the blood levels for thiamine were within the limits of normal variation. Guhr,[15] Ritsert,[35] Rowlands and Wilkinson,[38] Sinclair[41] found these limits to be between 3 and 16.5 micrograms per 100 cc. and as Guhr has pointed out, the physiologic variations are larger, since some apparently normal individuals have no more than a trace.

The daily urinary excretion of thiamine in our investigation was considerably lower than the normal levels given in the literature, in spite of the fact that the daily intake was adequate according to present standards. A number of investigators[8,27,28] found the normal 24-hour urinary excretion to vary from 60 micrograms to more than 100 micrograms. Patients suspected of thiamine deficiency excreted 5 to 70 micrograms daily.

The blood levels of riboflavin were within the limits of normal variation which were found to be from 0.35 to 0.5 micrograms/cc.[2,47] Daily urinary excretions of riboflavin were also within the reported limits of normal variation (500 to 800 micrograms).[40,47]

The blood plasma level of ascorbic acid in our subjects was generally low but nevertheless was mostly in the reported lower limits of normal variation. Several investigators[6,12,14,45,48] found the limits to be from 0.3 to 1.74 mg./100 cc. However, as pointed out by Storvic and Hauk,[45] "A mean plasma value which is indication of saturation for one subject may signify partial depletion of stores for another."

Although the average daily excretion of ascorbic acid in our subjects was rather low, it still was within the limits of normal variation reported. Levcovich and Batchelder[24] found it to be from 6 to 29 mg., with the intake ranging from 27 to 253 mg. Storvic and Hauk[45] reported an increase in the daily urinary ascorbic acid excretion from 26 mg. on a 50-mg. intake to 130 to 164 mg. on a 200-mg. daily intake.

In our experiment there was no correlation between the ascorbic acid intake and the blood plasma level or the urinary excretion of ascorbic acid. At the beginning of the second test period A. B. and W. N., because of the high petechiæ count, received a daily supplement of 130 mg. of ascorbic acid. The blood and urine analysis at the middle of the period did not show any response to this change. Because the petechiæ count of A. B. was still high, 195 mg. of ascorbic acid were added daily to her diet. This addition did not manifest itself in any way in the subsequent blood and urine analysis.

There was no correlation between the number of petechiæ and either the level of ascorbic acid in the blood plasma or the 24-hour urinary excretion. However, the number of petechiæ diminished with the increased dose of ascorbic acid. It is of interest to note that Levcovich and Batchelder[24] found that, "The capillary resistance was not significantly affected by varying the amount of crystalline ascorbic acid added to the vitamin C free diet."

The pantothenic acid content of plasma in our experiment was,

† 195 mg. synthetic ascorbic acid was added to the diet.

investigators. Most of the nicotinic acid values obtained were subnormal which is in line with the sub-standard intake of this vitamin.

There was no correlation between the intake of ascorbic acid and the level of this vitamin in the blood or its excretion in the urine. The 24-hour urinary excretions of ascorbic acid were normal, although rather low, in spite of a rather large intake of ascorbic acid supplement.

No correlation could be found between the number of petechiæ and the amount of ascorbic acid in the blood or its excretion in the urine. However, there was a correlation between the number of petechiæ and the amount of crystalline ascorbic acid added to the diet.

The 24-hour urinary excretions of riboflavin and of pantothenic acid were normal and that of nicotinic acid near the lower limits of the suggested normal range without any special supplements of these vitamins. The excretion of thiamine was definitely subnormal in spite of an adequate intake provided in part by thiamine chloride supplement to the milk-honey mixture.

The hyperemic condition of the gums observed during the test diet was probably not due to dietary deficiency. It could be explained by the physical character of the diet which did not provide for any mastication.

Conclusion. This diet proved to be adequate to support life, but not to prevent deficiency symptoms entirely.

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THE DEVELOPMENT OF PULMONARY TUBERCULOSIS IN CONGENITAL HEART DISEASE

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It is a commonly accepted premise that those individuals suffering from congenital heart disease, notably pulmonary stenosis, are particularly prone to develop, and later, to succumb to pulmonary tuberculosis. This premise is based chiefly on statistics compiled from case reports in the literature, 2 of the most complete tabulations being those of Norris[15] (1904) and Abbott[2] (1936). There are, however, few reports of specific cases in which congenital heart disease and pulmonary tuberculosis existed concomitantly, and fewer still which explain the evolution of the pulmonary infection in relation to the cardiac anomaly. It is the purpose of this study to investigate the frequency of congenital heart affections in a tuberculosis institution, to determine the type and course of the pulmonary disease and to evaluate the efficacy and advisability of collapse therapy in the face of the cardiac handicap.

Material. The material for the report includes 13 cases of congenital heart disease, upon 7 of which postmortem examinations were performed. These 7 cases were discovered during the course of 1545

examinations on tuberculous individuals, an incidence of 0.4%. This incidence may be higher than that encountered in other tuberculosis institutions since 250 of our 2000 beds are allotted to the pediatric service. It is considerably lower than that reported from institutions or services limited entirely to the treatment of children (5.5% Gelfman and Levine[10]). It is approximately the same in general hospitals, if deaths under 2 years of age due to congenital cardiac anomalies are excluded (0.5% Gelfman and Levine;[10] 0.4% Cabot;[5] 0.9% Rannels and Propst[16]).

Ten of our patients were males, 3 females, giving a ratio essentially the same as in our general autopsy material. It is interesting that 6 patients were of Italian descent. Since, however, we had no information concerning consanguineous marriages or other hereditary factors, it is impossible to suggest an explanation. There is no predominance of Italians in either our hospital census or our autopsy material.

Frequency. It is now almost 100 years since Rokitansky[18] observed that pulmonary tuberculosis and heart disease are incompatible, particularly when the latter is associated with cyanosis. He began a controversy which still continues. Most observers now insist that, since the cyanosis of pulmonary stenosis differs in its origin from that of acquired valvular lesions, the two diseases are not mutually exclusive and, in fact, that pulmonary stenosis actually favors the development of tuberculosis. In Abbott's[2] analysis of 1000 cases of congenital heart disease, 110 revealed pulmonary stenosis. Of these, 24 (22%) are listed as having tuberculosis. Of the remaining 890 cases with various types of congenital defect, 50 (5.5%) had tuberculosis. The next highest incidence of tuberculosis after pulmonary stenosis occurred in the group of 62 cases with interventricular septal defects (14.5%). Other authors report an incidence of pulmonary tuberculosis in pulmonary stenosis varying from 10% to 80%.[3,11,19,21] To assist in clarifying this question of incidence, we selected at random from the literature of the past 10 years, 50 cases of congenital heart disease, in which death occurred after 5 years of age and in which necropsy records were complete. In this group, 2 of 21 cases (9.5%) with pulmonary stenosis and 1 of 18 cases (5.5%) with interventricular septal defect succumbed to tuberculosis.

Our own cases support the view that patients with pulmonary stenosis are especially susceptible to pulmonary tuberculosis. All 7 of those which came to necropsy demonstrated this defect, in 5 of which it was associated with the other components of the tetralogy of Fallot. Of the 6 cases which were not autopsied, 3 were clinically diagnosed pulmonary stenosis. One of these was proved by contrast visualization of the cardiac chambers by the multiple fluorographic and motion picture technique and has been reported by Grishman, Steinberg and Sussman.[13] Of the remaining 3 cases, 1 had a patent ductus arteriosus and the others were diagnosed non-cyanotic congenital heart disease, without evidence of pulmonary stenosis.

Apparently, then, of all congenital cardiac anomalies those patients with pulmonary stenosis are most likely to develop pulmonary tuber-

culosis. Whether they are more likely to develop phthisis than are individuals with normal hearts is impossible to determine without additional statistical data. Since, the mortality rate from tuberculosis in the general population differs with age, sex, race, locality, and other factors, information regarding each of which is not available in the reported cases of congenital heart disease, there can be no basis for comparison of the two groups. The fact that our cases fall into a younger age group than is usual in our autopsy material indicates that there may be a measure of predisposition in patients with pulmonary stenosis. The youngest patient was 9, the oldest 60. Seven cases were from 4 to 20 years of age, a preponderance which is about a decade younger than the highest mortality usually reported from tuberculosis.[9]

Whether patients with this congenital anomaly are more likely to die of tuberculosis than any other catastrophe is a little easier to determine. In Stölker's[19] series, of those who lived beyond 19 years just as many succumbed to a cardiac death as to tuberculosis. In Abbott's group of 110, there were almost twice as many cardiac deaths as there were patients listed as having tuberculosis. She has noted[1] that the incidence of tuberculosis rises as the age group increases, an observation, however, which can be noted in any group of individuals. In the cases mentioned above which we have culled from the literature, death was due in many more instances to other causes, than to phthisis.

It is obvious, then, that while tuberculosis is a hazard to the patient with pulmonary stenosis, it is a no greater menace than his own cardiac defect. This fact also explains why the incidence of pulmonary stenosis in a tuberculosis institution is no higher, if as high, as in a general hospital. Many of these patients apparently succumb before they have an opportunity to develop tuberculosis or are so incapacitated by their cardiac defect that they are protected from infectious contacts.

Clinical Observations of Cardiac Disease. The symptoms and physical examination of the cardiovascular system in our patients were typical of the congenital defect found at autopsy examination, the specific defect being diagnosed correctly before death in every instance in which exact classification was attempted. With the help of Roentgenography and fluoroscopy the diagnoses were unusually accurate. Since most of these defects exemplified the tetralogy of Fallot a composite picture covers most points of interest.

Case Study. The patient is a white youngster in his lower 'teens. The history reveals cyanosis from birth or shortly thereafter with the diagnosis of congenital heart disease made in infancy or early childhood. The youngster has been placed on restricted or moderate activity, depending upon his subjective symptoms. He has been followed in a hospital out-patient department and has had at least one previous hospital admission for observation of the cardiac defect. There has been no evidence of congestive failure and he has led a fairly normal life until the onset of his pulmonary disease. Examination reveals an underdeveloped child who appears younger than his chronologic age. He is cyanotic and there is moderate to marked clubbing of the fingers and toes. Dyspnea is not marked. The heart is enlarged in all dimensions and there is a loud, harsh systolic murmur heard best at the base, usually associated with a systolic thrill. Abnormal findings in the lungs are dependent upon the pul-

monary pathology. Routine laboratory studies reveal a well-marked polycythemia and sputum is positive for tubercle bacilli. The electrocardiogram reveals right axis deviation with tall P waves, which are often notched. Roentgenography and fluoroscopy demonstrates enlargement of both left and right ventricles with frequently a sharply convex right border indicating marked enlargement of the right ventricle. The pulmonary conus is usually prominent. This is contrary to Grier's[12] observations, probably because his studies were made in a younger age group than ours. The venous pressure is within normal limits. The blood pressure tends to be normal or slightly decreased.

Up to this point, then, it is obvious that the pulmonary disease has not influenced the classical findings in cases of tetralogy of Fallot. The two cases exhibiting other cardiac anomalies, *cor biatriatum triloculare* and pulmonary stenosis with patent foramen ovale, likewise do not deviate from the typical pattern. It is interesting that the triloculate heart, as well as the case of tetralogy of Fallot that was proved by contrast visualization of the cardiac chambers, both demonstrated equal saccharine and ether circulation times. This has been suggested as a convenient method for determining the presence of an arteriovenous shunt (Grishman[13]). Unfortunately in only a few of our patients was this test performed. In one tetralogy of Fallot, the ether and saccharine times were 9 and 15 seconds respectively. In the case of patent ductus arteriosus they were 17 and 25 seconds respectively.

The vital capacity was not obtained in many of our patients, but where this determination was made, it was usually diminished but within normal limits. In the case of tetralogy of Fallot reported by Grishman *et al.*,[13] these authors found the vital capacity to be 3500 cc. This was before the onset of the pulmonary tuberculosis. A few months after onset, it had fallen only 300 cc. The lowest vital capacity in our series was in a patient with tetralogy of Fallot in which it was 950 cc. with a Peabody factor of 3, interpreted as 30% of the normal resting minute ventilation. This determination, however, was made following reëxpansion of a successful therapeutic pneumothorax, in which the collapsed lung was fibrotic and in which the contralateral lung was the site of a fresh spread. Vital capacities in other patients with the tetralogy of Fallot were 2500 (Peabody factor, 6), 2700 (Peabody factor, 7.9) and 2500 (Peabody factor, 5.2).

Cause of Death. Congestive failure was a prominent feature only in the case of patent ductus arteriosus. It was present in 3 other cases terminally or during the last few months of life. Bacterial endocarditis was found in 3 of the cases which were examined at postmortem, but was neither extensive nor even a contributory cause of death. Two of these cases had fibrinous pericarditis, 1 of minimal and the other of moderate degree. With the exception of 1 case which succumbed from extension of a previously resected brain tumor, the immediate cause of death in all our patients was progressive pulmonary tuberculosis. In 3 cases who died but did not come to autopsy, the progressive pulmonary involvement was likewise the apparent determining factor terminally.

The Pulmonary Aspect. In 4 of the 13 cases the presence of close contact of the patient with an open case of pulmonary tuberculosis

was established. In 2 other cases there had been frequent hospitalizations on general wards, which may have been an exposure factor. In any event, at least 4 of our patients had a good chance to develop tuberculosis irrespective of their cardiac condition. In the literature there is ordinarily no notation made of contacts, whether absent or present. When such observation is made, it is usually in the negative.[4,8]

The onset of pulmonary disease in our cases was similar to that of patients without congenital heart disease. In 3 cases the tuberculosis was ushered in with hemoptyses, although in none of these had hemoptyses previously been a part of the cardiac picture. In 1 case hemoptyses had been present for several years before and up to the onset of tuberculosis and it was impossible to determine the etiology of the later bleeding, whether cardiac or pulmonary. In another case, hemorrhage had been a prominent feature in the boy's earlier life, but had ceased several years before the onset of the pulmonary infection. Whether or not an hemoptysis was the presenting symptom of the tuberculosis, some or all of the usual symptoms of this disease were always present. Weight loss, night sweats, easy fatigability, fever, productive cough, and chest pain were present in varying degrees in each case. The severity of these symptoms was necessarily influenced by the degree to which they had been present due to the cardiac disease. The fatigability was greater than the patients had usually experienced. Chest cardiac pain when present previously became lancinating in character and was influenced to a greater extent by respiration. If a chronic cough were present, it became productive of purulent sputum. In no case did the patients notice at the onset of the pulmonary infection an increase in their dyspnea and cyanosis.

The difficulty of differentiating between congenital heart disease and pulmonary tuberculosis and in diagnosing the latter in the presence of a cardiac lesion has been stressed in some of the studies of the two diseases.[7] Such difficulty was not encountered in our cases, since the congenital anomaly was diagnosed in all cases many years prior to the onset of the pulmonary infection, which was recognized fairly promptly at its onset. This is probably due to the fact that many of these patients were followed closely from the cardiac aspect with frequent fluoroscopic examinations. In spite of this fact, the pulmonary disease on admission, in all but 1 case, was a moderately or far-advanced one, as is true of most of our admissions.

The course of the disease was also similar to that observed in most of our patients who are admitted without the added cardiac hazard. The duration of life apparently depended, as in all tuberculous patients, upon the extent of the disease on admission and the effectiveness of collapse therapy, when that form of treatment was utilized. A glance at Table 1 will reveal how little the length of life depended upon either the age of the patient, the congenital abnormality, or the presence of cyanosis. The longest duration (6 years) was in a boy of 15 with the tetralogy of Fallot who had marked cyanosis from birth. The shortest courses (7 months) were in a man of 27 with the tetralogy

of Fallot and cyanosis since birth and a boy of 21 with a *cor biatriatum tricoculare* and cyanosis from the age of 4 years. The average duration of life from the onset of the pulmonary infection to exitus was 1 to 2 years.

TABLE 1.—ANALYSIS OF CASES

Case	Sex	Age	Abnormality	Cyanosis	Duration of Tb.	Pneumothorax	Congestive failure	Outcome
1	M	9	Tetralogy of Fallot	Marked from 4 yrs.	2 yrs.	0	0	Autopsy
2	M	14	Tetralogy of Fallot	Marked from 1 yr.	9 mos.	0	0	Autopsy
3	M	21	Cor biatriatum triloc.	Marked from 4 yrs.	7 mos.	0	Present	Autopsy
4	M	11	Tetralogy of Fallot	Marked from birth	15 mos.	0	0	Autopsy
5	M	15	Tetralogy of Fallot	Marked from birth	6 yrs.	Effective	0	Autopsy
6	F	11	Tetralogy of Fallot	Moderate	16 mos.	Ineffective abandoned	0	Autopsy
7	F	21	Pul. stenosis and patent for. ovale	Terminal	4 yrs.	Ineffective; abandoned	Terminal	Autopsy
8	M	33	Pat. ductus arteriosus	On exertion	1 yr.	0	Present	Discharged; arrested
9	M	60	Congenital heart dis.	Minimal	3 yrs.	0	Present	Signed out; improved
10	M	19	Prob. pul. stenosis	On exertion	5 yrs.	Ineffective; abandoned	0	Signed out; unimproved
11	M	27	Tetralogy* of Fallot	Marked from birth	7 mos.	0	0	Died; progressive pulm. Tb.
12	M	19	Prob. tetralogy of Fallot	Marked from birth	2½ yrs.	Ineffective; abandoned	0	Died; progressive pulm. Tb.
13	F	16	Congenital heart dis.	On exertion	8 mos.	0	0	Died; progressive pulm. Tb.

* Proved by contrast visualization of cardiac chambers (Grishman *et al.*[13]).

The pulmonary tuberculous lesions, as well as the type of onset and course of the disease, were similar to those usually observed in our autopsy material. In every case which came to necropsy, there was a typical adult type, chronic pulmonary tuberculosis of the lungs with numerous excavations, frequently interlocking, areas of caseous lobular pneumonia, and bronchogenic acinous nodose spread to most or all lobes. Gastro-intestinal involvement with tuberculous ulcerations, which we have usually found in this type of pulmonary disease, was present in 6 of the 7 cases. Laryngeal tuberculosis, which we have also found a frequent though later associate of chronic pulmonary tuberculosis, was present in 2 of the 7 cases.

As the lesions and other factors of the pulmonary infection are the same, whether or not the patient has congenital heart disease, and as the cause of death depends rather on the pulmonary than on the cardiac status, it is the lung rather than the heart which should be the focal point of therapy. Bed rest may be sufficient treatment for the lung and useful to the heart, but when it fails to arrest the progression of the tuberculous infection or cannot accomplish cavity closure, it must in spite of the heart be supplemented by collapse therapy. Frequently such therapy has been postponed, not because the pulmonary involvement was unsuitable for collapse, but because the clinician was reluctant to place an added burden on the defective cardiac system. When instituted late in the course of the disease, collapse therapy is neces-

sarily a "do or die" procedure and the possibility of arresting the course of the tuberculosis is doubtful indeed. Admittedly, the life expectancy in these patients, even without the added pulmonary com-

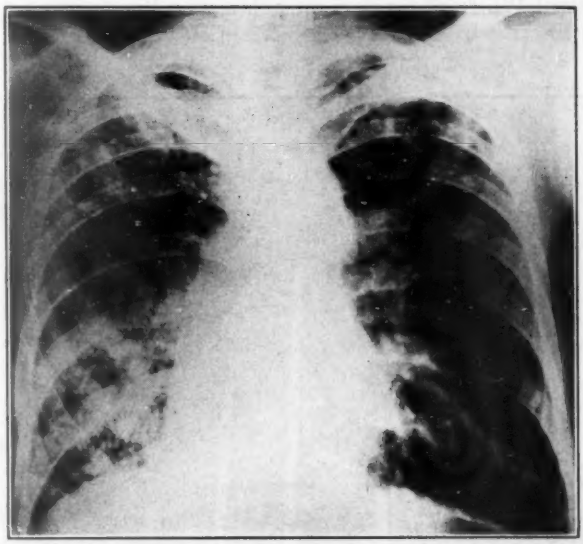

FIG. 1.—Case 3. Chest roentgenogram 1 month before death. Bilateral upper lobe excavations with extensive bronchogenic spread throughout the right lung. Prominence of the aortic knob. Straight right cardiac border.

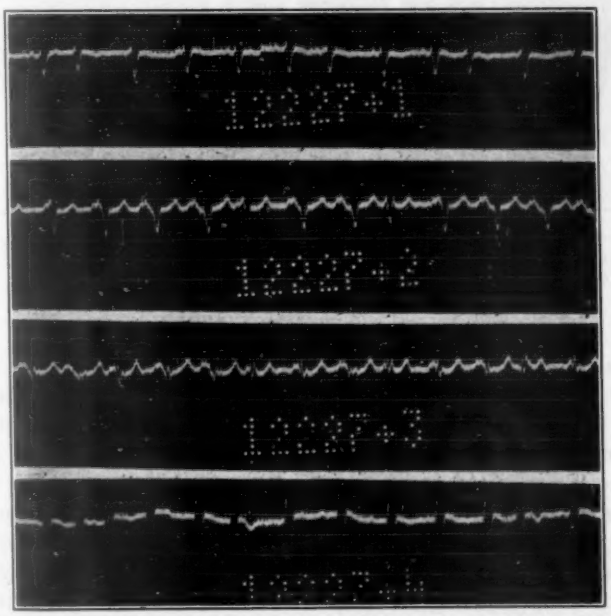

FIG. 2.—Case 3. Electrocardiogram 2 weeks before death. Right axis deviation. P waves notched. Many premature contractions.

plication, is short. Nevertheless, measures which may be taken to prevent the patient from succumbing to tuberculosis, although they may be hazardous ones, seem justified. Because these patients are tuberculous is no reason why they cannot be given the opportunity to emulate Paul White's[22] famous musician who lived with a tetralogy of Fallot into his 60th year.

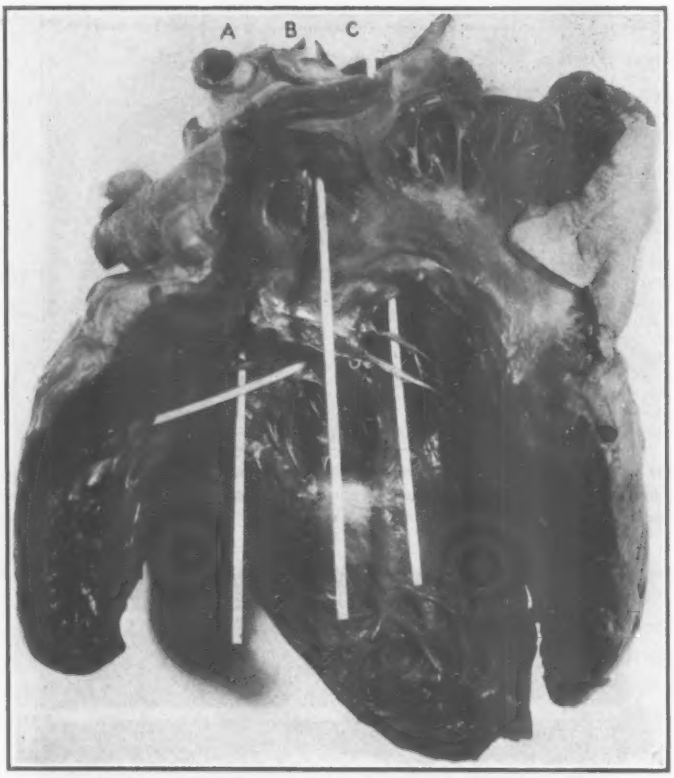

FIG. 3.—Case 3. Complete absence of the interventricular septum. Probe *A* passes from the ventricle into the pulmonary artery. Probe *B* passes through the widely patent foramen ovale. Probe *C* passes from the ventricle into the aorta.

This attitude towards active therapy is reflected in the literature of the past 10 years. Ritschel[17] in 1932 reported a case of pulmonary stenosis with marked cyanosis in which he instituted pneumothorax and secured cavity closure and arrest of the tuberculous infection. He noted no increase in the clinical signs of heart disease after the induction of pneumothorax and concluded that congenital pulmonary stenosis was not a contraindication to this form of therapy. Hillesheim[14] also induced pneumothorax in cases with pulmonary stenosis and secured satisfactory results without cardiac complications. We have discovered no case in the literature in which thoracoplasty was done to control the pulmonary lesion.

In our cases pneumothorax was instituted in 5 cases. In 3 of these the pneumothorax was abandoned as ineffective because of adhesions which could not be severed by closed pneumonolysis. In 1 case the pneumothorax was abandoned because of adhesions and the develop-

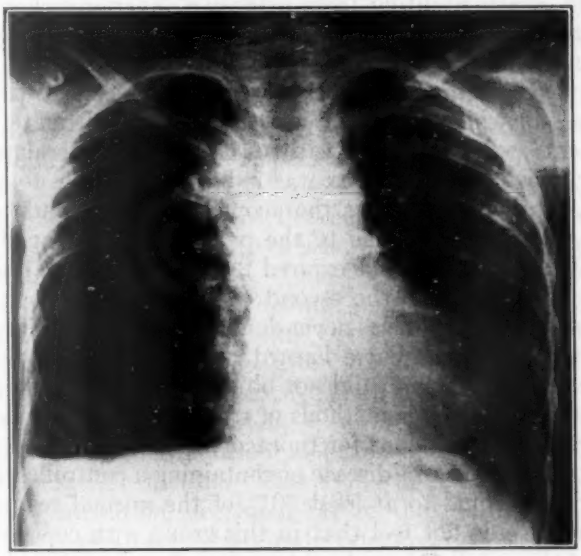

FIG. 4.—Case 5. Chest roentgenogram. Lesion on the right controlled by pneumothorax. Excavations in the left upper lobe. Heart is boot shaped. Fluoroscopy revealed the bulge on the right to be pulsating, apparently ascending aorta.

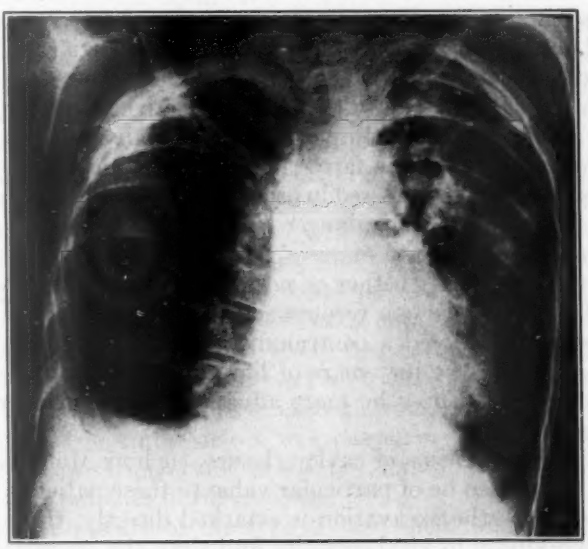

FIG. 5.—Case 5. Chest roentgenogram 5 years later. Right lung has been expanded and postmortem examination revealed a healed excavation. There has been progression of the lesion on the left.

ment of empyema. In this same case pneumothorax was induced on the contralateral side, as a last resort measure, and death occurred too soon after induction to accomplish cavity closure. In 1 case pneumothorax accomplished good results and the lung was reëxpanded. Postmortem examination revealed a closed cavity on the pneumothorax side, death resulting from extensive cavernous disease in the contralateral lung. In no case did collapse therapy increase the cardiac symptoms or lead to congestive heart failure.

In reviewing the therapy which our patients received, there are at least 2 cases in which treatment was probably inadequate. Both of these patients were admitted with essentially unilateral pulmonary disease for which pneumothorax was induced, but later abandoned as ineffective. In the first case a thoracoplasty was then advised. The procedure was not acceptable to the patient, he developed a spread in the contralateral lung and expired 2½ years after the onset of the pulmonary infection. In the second case, a thoracoplasty was considered, but the operation was never done because the cardiac condition was thought to be too great a hazard. It is interesting that in this case, the cardiac consultant did not object to the major surgery, provided no other less drastic methods of treatment were available.

In general, the indications for thoracoplasty in our hospital include a contralateral lung free of disease or containing a controlled lesion and a vital capacity equal to at least 50% of the normal resting minute ventilation. We do not feel that in this group with congenital heart disease that these indications should be altered, unless there is evidence of congestive cardiac failure. The immediate postoperative condition will always depend upon the degree of shock, the paradoxical respiration, diminution of vital capacity and spread of disease from aspiration of infected material. The first two complications can be treated. The third need not necessarily be great, since the portion of lung which is collapsed is to a large extent useless as respiratory tissue due to the disease process. In any case, this selective type of collapse is probably more nearly accomplished with a thoracoplasty than a pneumothorax, since in the latter, large portions of good pulmonary tissue must often be compressed in order effectively to close excavations elsewhere in the lung. The danger of contra- or homolateral spreads from aspiration of infected material is always present and, to a large extent, uncontrollable, whether or not a cardiac lesion is present. In view of these facts, we can recommend that congenital heart disease should not be considered a contraindication to thoracoplasty and in order not to waste the few years of life expectancy of these patients immediate operation may be more advantageous than a preliminary trial of pneumothorax.

The newer mechanisms of cavity closure, such as Monaldi and cavernostomy, may also be of particular value to these patients. In these procedures where the excavation is attacked directly, there is practically no diminution in vital capacity and since the operation is not a formidable one, there is no shock. The dangers of spread are also minimized since there is a direct drainage of infected material from

the cavity. However, these techniques are too new to permit adequate evaluation and certainly not all types of cavernous disease are suitable for these methods of attack.

The Physiologic Relationship of a Pulmonary and Cardiac Disease. Since we do not have sufficient knowledge to determine all the factors necessary for the development of tuberculosis in individuals with normal cardiovascular systems, speculation concerning how and why it develops in patients with congenital heart disease must necessarily be nebulous. Factors leading to the greater susceptibility to tuberculosis of patients with pulmonary stenosis have been variously stated to be due to anemia of the pulmonary vascular bed; lowering of resistance due to the accumulation of the toxic products of metabolism that escape oxygenation; the life expectancy which extends to the age group most susceptible to tuberculosis;[1] and the unequal pulmonary and bronchial circulations.[15]

As, however, there are certain definite metabolic characteristics in the hemorespiratory exchange in morbus cæruleus one is forced to the conclusion that, whatever predisposition to tuberculosis exist in these cases, it must be based primarily upon those changes. Talbott, Coombs, Castleman, Chamberlain, Consolazir and White[20] in 1 case, and Campbell, Hunt and Poulton[6] in 3 cases of morbus cæruleus, found consistent metabolic factors. There was an increased O_2 capacity, decreased O_2 saturation, decreased carbon dioxide content, decreased partial pressure of alveolar carbon dioxide, and decreased arterial pH. The acidosis is particularly interesting since it was probably due chiefly to the concentration of acids in the blood, acids which are not definitely identified, but which are organic and in all likelihood the toxic products of metabolism.

Although metabolic studies were not as complete in our cases as in those mentioned above, those that were done agree with the findings of these authors. In 2 cases with the tetralogy of Fallot the arterial oxygen was 26 cc. and 23 cc. per 100 cc. of blood respectively. The arterial carbon dioxide was 34 cc. and 34.6 cc. per 100 cc. of blood. In 1 case of pulmonary stenosis the arterial oxygen was 25 cc. and the carbon dioxide was 42. Since these changes are so typical of this group of cases, their apparent susceptibility may well be due to this variation from the normal. Exactly how this predisposition functions and in what respect the altered tissue physiology furnishes suitable culture media for the tubercle bacillus is impossible to determine.

Summary and Conclusions. A study has been made of 13 patients who had congenital heart disease and contracted pulmonary tuberculosis, upon 7 of whom postmortem examinations were performed. The most common congenital defect was pulmonary stenosis, which was present in all cases which came to autopsy, implying a certain predisposition of these patients to tuberculosis.

A composite picture of the typical case, including clinical, physiologic and pathologic studies, has been presented. From this material we may conclude that the pulmonary tuberculosis runs a course typical of that disease, irrespective of the cardiac lesion. The functioning of

the defective cardiac system is affected unusually little by the superimposed respiratory infection.

In view of this observation, together with the fact that our patients succumbed to the pulmonary involvement rather than failure of the defective cardiovascular system, active treatment of the tuberculosis is recommended. Pneumothorax induced in 5 of our patients did not lead to congestive heart failure in any instance. The importance of other surgical forms of collapse therapy for these patients has been discussed.

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A CASE OF HISTOPLASMOSIS IN AN INFANT WITH AUTOPSY

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At the time of Darling's[1] first description of histoplasmosis (1906), he thought that the infectious agent was a protozoan related to members of the genus Leishmania. In 1934 Dodd and Tompkins[2] from Tennessee announced the 6th case on record and supplied DeMonbreun with material from which he cultured the organism.[3] Though appearing as a yeast form in the human host, on artificial media it grew as a

mass of matted mycelial threads with prominent chlamydospores. Thus was disproven the protozoan etiology of this disease which even today startles the pathologist from the humdrum of routine by its resemblance to kala-azar. In 1939 the number of cases recorded had risen to 12 and by 1941 had reached a total of 32. At present over 50 have been reported, ranging widely in geographic distribution, as well as in age and sex incidence.

In a recent report VanPernis, Benson and Holinger[4] summarized the various pathologic lesions found in the disease and added a case of their own in which the presenting symptoms were produced by invasion of the larynx. Prominent in all is involvement of the hemolytopoietic system: the lymph nodes, particularly the cervical, tracheobronchial, mesenteric, and periaortic nodes; the follicles of the lungs and gastro-intestinal tract; the spleen; and the bone marrow. In these structures the mononuclear and endothelial cells are heavily parasitized. The liver is usually enlarged, the parenchymatous as well as the Kupffer cells contain the fungus. Invasion of either or both the cortex and medulla of the adrenal glands is not uncommon. Less frequent is involvement of the heart, kidneys, thymus, pancreas, skin, meninges, pharynx, and joints.

Grossly as well as microscopically the lesions resemble those of tuberculosis; a central area of necrosis surrounded by large monocytes and lymphocytes. The Langhans giant cells are usually absent. The presence of the yeast form of *Histoplasma capsulatum*, usually most numerous in the monocytes, is the outstanding distinguishing characteristic. The present case conforms well with the "typical" pathologic picture as developed during the past decade. The only unusual feature is the extreme youth of the patient.

Case Report. A boy, 7 weeks old, was admitted to the hospital and died 2½ weeks later. Delivery had been normal after 8 months gestation, weight at birth being 5 pounds. Though never breast-fed, in growth and appearance the child seemed healthy. Admission was advised for treatment of a hydrocele of the right testicle. The family history contributed no relevant data.

On inspection, the child was a small male weighing 7 lbs. 7 oz., the skin pale but not icteric, the superficial abdominal veins very prominent, and the abdomen protuberant. He seemed very irritable and cried readily when picked up or disturbed. The rectal temperature was 101.4° F., the pulse and respirations were rapid. The mucous membranes were pale; the nose, throat, and ears not abnormal. The breath sounds were harsh, but no râles and no changes to percussion were noted. The heart was apparently normal. The liver and spleen were both enlarged; the tip of the spleen could be felt almost at the pelvic brim. There was a small umbilical hernia and a right-sided hydrocele the size of a walnut.

Diagnosis: bronchitis and secondary anemia, with associated splenomegaly and hepatomegaly of unknown origin.

The red cell count was 2,400,000, hemoglobin 7.5 gm., platelets 97,000, leukocytes 6100 (20% neutrophils, 77% lymphocytes, and 3% monocytes). Three normoblasts were found, as well as moderate anisocytosis and poikilocytosis. The urine contained a faint trace of albumin and 3 to 8 leukocytes per high-power field. The blood Wassermann test was negative, as were also stool cultures for typhoid and dysentery organisms. A bone marrow smear on the 7th hospital day did not show any abnormal cells. Roentgen ray of the chest revealed no change in the normal appearance of the heart or lungs.

The child had increasing difficulty in breathing and did not take its formula well. Regurgitation after feeding was frequent and several times this was accompanied by attacks of cyanosis. The temperature was never below 100° F. and usually remained about 102° F.; the pulse and respirations were very rapid. After two transfusions of citrated whole blood the hemoglobin rose to 12 gm., the red cell count to 3,660,000 and the leukocytes to 5800 (40% neutrophils, 60% lymphocytes). The number of platelets reached 175,000. At no time did the child show any frank bleeding, but minute petechiæ were observed on the buttocks and chest about 14 days after admission. On the 16th day a splenic puncture was performed and smears made of the aspirated pulp. Histoplasmosis had not been suspected but examination of the smears prepared with the usual Wright stain revealed the typical yeast forms of the fungus in the monocytes (Fig. 1). On the following day another tibial marrow study was made and the same bodies seen in the direct smear. At this time also, another splenic puncture was performed and the marrow and splenic pulp streaked on blood agar plates from which the organisms were subsequently isolated in pure culture. The child died 18 days after admission and 2 days after the diagnosis of histoplasmosis was made, at the age of 9½ weeks.

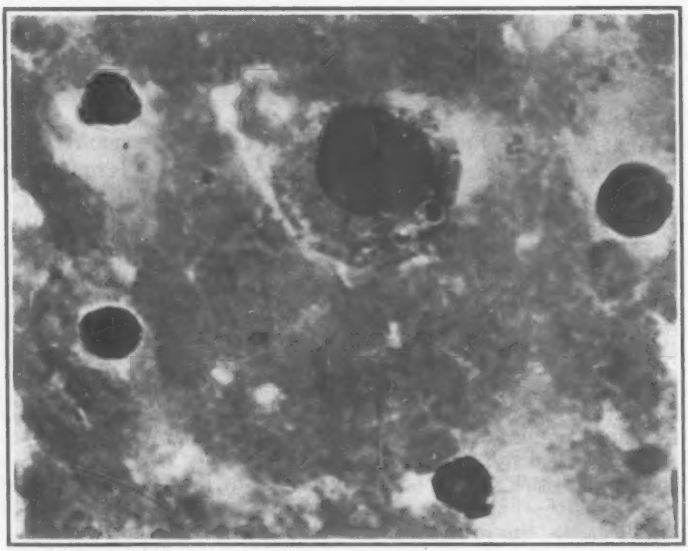

FIG. 1.—Smear of material obtained by splenic puncture. In the center of the field is a monocyte containing two yeast forms of *Histoplasma capsulatum*. (Wright stain. × 1200.)

Autopsy (1 hour after death). The body weighed 2500 gm. and showed marked evidence of emaciation. The abdomen was distended and large veins were visible beneath the skin. Numerous pale petechiæ were scattered over the trunk; there was no jaundice, cyanosis, or edema. The spleen was palpable almost to the crest of the ilium, the liver extended 2 cm. below the costal margin. Internal examination revealed transparent and glistening pleuræ with no free fluid in either pleural space. The peritoneum was likewise smooth, the stomach and intestine moderately distended with gas. The spleen was visible, occupying much of the left half of the abdomen (Fig. 2). The leaves of the diaphragm had their normal position and the urachus, umbilical veins, and umbilical artery were occluded. The normal visceral relations were maintained and no gross congenital anomalies were present. The pericardium was thin, the serosal surfaces shining; the sac contained 0.5 cc. of clear yellow fluid.

The heart weighed 10 gm., the epicardium was smooth, no petechiæ were present. The myocardium was firm, uniformly red-brown in color. All the chambers were slightly dilated and contained a small amount of cruor. No congenital anomalies were demonstrable. All 4 valves were apparently normal, the papillary muscles well developed, the chordæ tendineæ long and slender. Histologically the myocardium was normal. The coronary vessels and aorta exhibited no abnormalities.

FIG. 2.—The sternum, heart and lungs have been removed, the liver displaced into the chest cavity. At the upper end of the incision a group of enlarged lymph nodes can be recognized; the spleen, though still attached to its pedicle, has been brought into view. The white ruler has a length of 8 cm.

The right lung weighed 13, the left 12 gm. Both organs were pale pink and almost emphysematous in consistency. On section, the upper portion of the right lower lobe contained 4 well-circumscribed, spherical, firm, yellow nodules ranging from 3 to 8 mm. in diameter. The parenchyma surrounding these nodules was essentially normal. No consolidated areas could be demonstrated elsewhere in the lungs, nor could pus be expressed from the bronchioles. The vessels were free of thrombi. Both grossly and under low magnification the nodules resembled those of tuberculous granulation tissue (Fig. 3). There was a large central area of necrosis surrounded by closely packed macrophages nearly all of which contained the yeast form of *Histoplasma capsulatum*. In

the cytoplasm of these cells, as elsewhere in the tissues, the fungus when stained with iron hematoxylin appeared as a spheroidal, refractile body, 2 to 4 μ in diameter, containing a dark blue-black granule usually 1 μ in diameter, the whole surrounded by a clear zone, the capsule. Throughout the lung there were focal collections of parasitized monocytes most often grouped about blood-vessels or lymphatics. However, the endothelial cells of the alveolar septa were often similarly involved for some distance from any large vessel (Fig. 4). A patchy monocytic infiltration was also present beneath the visceral pleura.

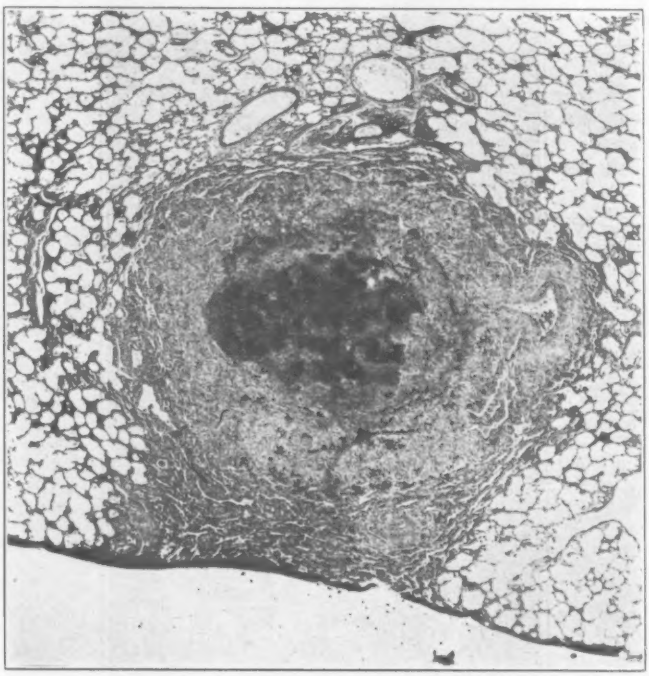

FIG. 3.—A nodule in the lung, illustrating the resemblance of these lesions to a tubercle. A central area of necrosis is surrounded by dense masses of monocytes which have reached the pleura and spread out beneath it. (Iron hematoxylin. × 30.) (U. S. Army Medical Museum Neg. No. 74909.)

The spleen weighed 80 gm., had a smooth surface, and a slate-gray capsule free of adhesions. The organ was firm, cut with usual resistance, and had a dark purple pulp that did not scrape away readily on the knife edge. Follicles and trabeculæ were indistinct. The mononuclear cells of the Malpighian corpuscles as well as those of the red pulp contained many of the yeast forms. In spite of the widespread involvement of the organ there were no focal areas of necrosis.

Each kidney weighed 20 gm., was of normal shape, size, and consistency. The capsule stripped readily, revealing a smooth pink surface on which the normal fetal lobulations were distinct. On section the cortex was 5 mm. in width, the cortico-medullary markings distinct. The pelvic mucosa of both organs was smooth and white. Microscopically, the kidneys were apparently normal. The mucosa of the ureter and bladder was everywhere white and intact. However, histologic examination revealed small focal collections of monocytes containing the parasite in the submucosa of the urinary bladder. Except for a right-sided hydrocele, the genitalia were apparently normal.

The serosa of the gastro-intestinal tract was everywhere smooth and gray-pink in color. The stomach contained about 6 cc. of partially clotted milk; the mucosa was rugose and free of ulceration. The mucosa of the small intestine showed the normal changes characteristic of the different regions, though Peyer's patches in the ileum were more prominent than usual. No enlargement of the solitary follicles of the large intestine was noted, nor was there blood anywhere in the lumen of the gastro-intestinal tract. The monocytes present in the lymph follicles of the small and large intestine contained many of the yeast forms of the fungus.

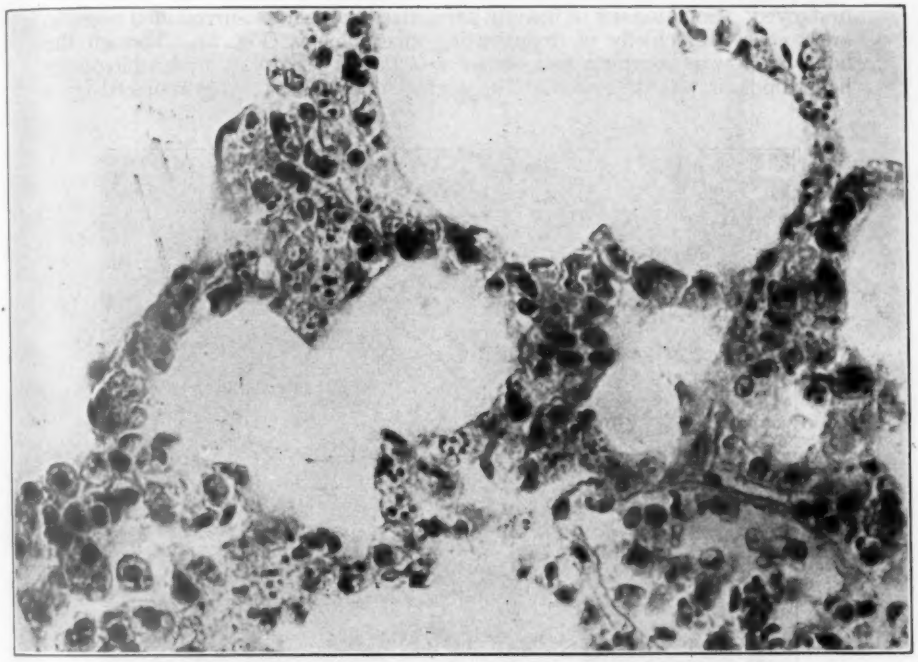

FIG. 4.—A region of the lung some distance from any discrete nodule. The endothelial cells of the capillaries in the alveolar walls contain many of the parasites. (Iron hematoxylin. × 810.) (U. S. Army Medical Museum Neg. No. 74904.)

The liver was enlarged (weighed 160 gm.). The surface was smooth, the capsule thin and transparent. On section the parenchyma was a mottled red-brown in color and blood oozed from the severed vessels. The cords of liver cells were separated by a rather loose connective tissue which was also increased in the portal areas. The cytoplasm of the liver cells was granular and only a few contained the parasites; occasional Kupffer cells were crowded with histoplasma. No areas of pseudotubercle formation were present. The small tubular gall bladder had a thin wall, velvety mucosa, and smooth serosa. Dark green viscid bile flowed readily through the ducts and the ampulla of Vater. Histologically the gall bladder was normal.

The pancreas was firm, pink-brown in color, and distinctly lobulated. The surrounding fat was free of necrosis or hemorrhage. No yeast forms were found in the parenchyma, though an immediately adjacent lymph node was heavily parasitized. The adrenals were relatively large, as is normal for an infant of this age. The cortex contained several bright orange granules, the medulla was firm and gray. Microscopically, the cells of the medulla were unexpectedly found to contain many histoplasma, though the cells of the cor-

tex were free. The thymus reached and partly covered the upper portion of the pericardial sac; yet, it was of approximately normal size for the age of the infant. It was soft, dark red and translucent. The lymphocytes were partly replaced by monocytes which in some regions formed focal collections the centers of which showed early necrosis. The monocytes contained many parasites.

The para-aortic lymph nodes in the region of the arch and those surrounding the trachea were matted together in a moderately firm mass. All of these nodes were enlarged and on section were rather opaque, orange-yellow in color. The lymph nodes of the mesentery were likewise enlarged, but translucent and gray-pink. The architecture of the involved nodes was completely destroyed. Solid masses of heavily parasitized monocytes surrounded necrotic areas consisting chiefly of degenerating macrophages (Fig. 5). Though the bone marrow of sternum and femur was bright red in color, histologically hematopoiesis was depressed. The normal marrow cells were replaced by a

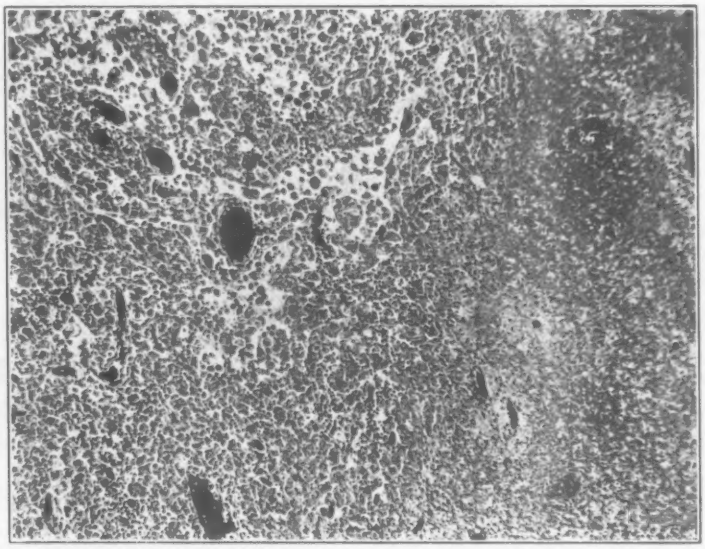

FIG. 5.—Section of lymph node showing a complete loss of normal architecture. On the right the tissue is necrotic, on the left the stroma has been infiltrated by large monocytes which on close inspection are seen to be heavily parasitized. (Iron hematoxylin. × 72.)

loose areolar connective tissue in which the blood sinuses were preserved, accounting for the red color on gross examination. Isolated islands of cells contained a few megakaryocytes, myelocytes and erythroblasts, but mature polymorphonuclear leukocytes and plasma cells predominated. No mitotic figures were seen. Occasional monocytes and endothelial cells contained a few yeast forms. In blood smears made at this time the large monocytes were likewise parasitized, though this had not been demonstrable in the circulating blood 2 days before death.

Punctate hemorrhages were present in the falx cerebrum and in the tentorium. No tears, however, were present in any of the cerebral membranes. The gross appearance of the brain was essentially normal, the convolutions complex, the sulci deep. Microscopic examination revealed no abnormal cellular infiltrations. In sections of the skin collections of monocytes containing the histoplasma were found in the loose fatty areolar tissue beneath the corium.

Cultural Studies. Material obtained from the spleen and tibial marrow by needle biopsy was streaked on blood agar plates and kept at room temperature. Growth was very slow but after 3 weeks white cotton-like colonies 2 to 3 mm. in diameter began to appear. These were transplanted to Sabouraud's medium where growth was more rapid and the colonies developed their characteristic faint buff color and slightly crinkled margin (Fig. 6). Microscopically they consisted of mycelial threads and prominent spherical chlamydospores. One culture, originally streaked on a blood agar slant and sealed with paraffin, showed minute white colonies scattered over the surface when examined 9½ months later. Microscopically, these consisted solely of the yeast form similar to that found in the tissues. When inoculated on Sabouraud's agar

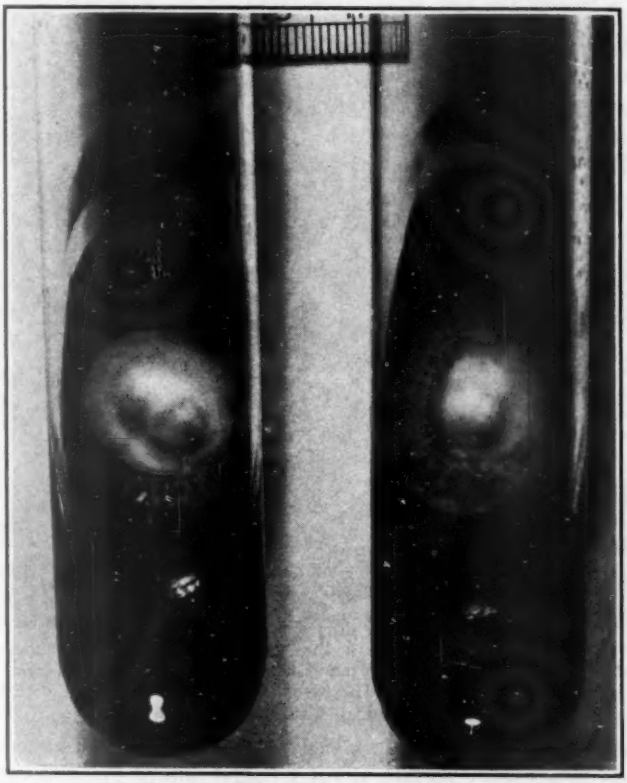

FIG. 6.—Growth of *Histoplasma capsulatum* in the mycelial form on Sabouraud's culture medium. (Natural size.)

these developed into the typical mycelial colonies. Splenic tissue and bone marrow removed at autopsy failed to yield colonies after inoculation on both blood agar and Sabouraud's medium.

Animal Inoculation. When the cultures were 6 weeks old, some of them were ground up in sterile saline and injected into the tail veins of 6 mice and the peritoneums of 6 rats. Three mice died after a few days and were negative on examination. The 3 remaining mice died within 3 and 4 months of inoculation. All showed a generalized lymph node involvement characterized by great enlargement and central necrosis. The histologic picture was similar to that found in the human lesion. Outstanding was the enormous size of the liver which in each animal almost filled the abdominal cavity. The surface

was smooth, but scattered over it were many minute yellow patches. Microscopically, the Kupffer cells were found to be almost solely involved. They were greatly enlarged and crowded with 20 to 30 of the yeast forms. The blood channels were almost obstructed and the cords of liver cells had undergone pressure atrophy (Fig. 7). The liver cells themselves were rarely parasitized.

The spleen was enlarged, the follicles and trabeculæ could not be recognized. Histologically, the normal architecture had been destroyed by a diffuse dense infiltration of monocytes. These cells together with the endothelial cells of the sinusoids contained large numbers of *Histoplasma capsulatum*. Although

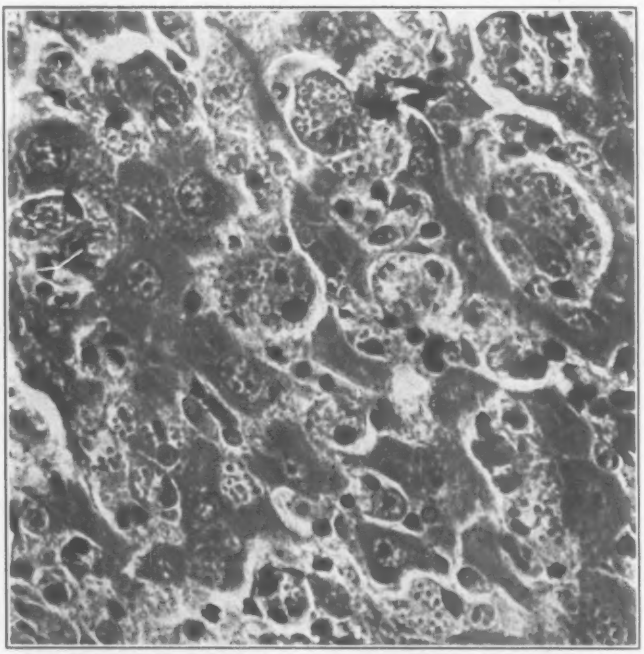

FIG. 7.—Section of liver from a mouse that died 3½ months after inoculation. Each Kupffer cell contains 5 to 30 yeast forms of the fungus and are so enlarged that they almost occlude the blood sinusoids. The cords of liver cells are atrophic. (Iron hematoxylin. × 810.) (U. S. Army Medical Museum Neg. No. 74905.)

the kidneys were grossly normal, the endothelial cells of the glomerular capillaries were distended by the parasites and the flow of blood must have been greatly impeded. The endothelial cells of the pulmonary capillaries were likewise heavily parasitized.

After 8 months the rats, which had been inoculated intraperitoneally, were quite healthy. They were sacrificed and on gross as well as microscopic examination failed to reveal any pathologic changes.

Discussion. Histoplasmosis is primarily a systemic disease of the lymphoid tissue, characterized by the presence of large numbers of the yeast form of *Histoplasma capsulatum* in the monocytes and endothelial cells of the lymph nodes and spleen. Careful search will usually reveal the parasite in collections of lymphoid tissue in other organs, such as the lungs, intestinal tract, and skin. The parenchymal cells of the

liver and adrenals are frequently involved, and in the case reports now on record nearly every organ has at one time or another been found to harbor the fungus.

At least 5 cases of this disease occurring in infants or young children are recorded, but to our knowledge this is the youngest, death resulting at the age of 9½ weeks. For the first 2 weeks of life the child remained in a large city hospital following which it was at home only a month before being brought to another hospital in the same city. It is probable that the disease was contracted during that month. The infant was never breast-fed, but the source and mode of infection is unknown.

Summary. A 7 week old infant was admitted with signs of anemia, splenomegaly and hepatomegaly. The diagnosis of histoplasmosis followed finding the parasite in material obtained by splenic puncture. This was proved by subsequent culture and animal inoculation.

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THE RELATION OF VITAMIN B TO THE TOXICITY OF PROMIN AS TESTED BY THE SELF-SELECTION METHOD

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(From the Division of Experimental Medicine, Mayo Foundation)

Promin (sodium p, p′-diaminodiphenylsulfone-N, N′-didextrose sulfonate) exerted certain rather severe toxic influences when it was administered orally to guinea pigs.[6,8,9] These changes included hyperirritability of the animal, severe paralysis of the hind limbs, considerable anorexia and cyanosis. Toxic influences were exerted on the erythrocytes, resulting in their crenation and subsequent removal from the blood stream. As a result, hypochromic anemia, with many of the features of true hemolytic anemia, developed. Abnormal discoloration of the tissues was the result of changes induced in the hemoglobin of the erythrocytes, giving rise to methemoglobin and sulfhemoglobin.[18] These changes were reversible. The bone marrow, as a result of destruction of blood, became hyperplastic and macrocytosis, polychromatophilia and reticulocytosis became characteristic features in the peripheral blood, even in the presence of high concentration of promin in the blood.

In an attempt to study factors which might well alleviate some of the toxic reactions observed therapeutically, the white rat was selected as the animal best suited for further experimental work of the sort contemplated. The rat reacts to promin in ways quite like those of the guinea pig and thus is a most satisfactory test animal. Since certain studies had shown that the toxic effects of some of the sulfon-

amide compounds were mitigated either by the fractions of vitamin B or by diet,[10] I studied the reactions to promin in growing white rats which were fed purified diets, with and without constituents rich in the vitamin B complex. In addition, I studied these toxic reactions in rats which were permitted to imbibe freely the better known fractions of the B complex, provided in suitable water bottles attached to their cages. In a series of studies on the self-selection method, Richter and his colleagues[13–17] described results which indicate the capacities of rats to select adequately the foods, minerals and vitamins required.

This report covers my study of the reactions elicited in white rats by the daily oral administration of promin for 21 days, during which time they were free to help themselves to such fractions of the B-complex as were desired.

Method of Study. My initial observations were made on rats housed in small metal cages to which the bottles containing the water-soluble vitamins were attached. I first observed that the rats drank largely from the thiamine bottle after the oral administration of promin. Although the position, on the cage, of the bottle containing the thiamine was changed frequently, I could not help but believe that chance may have operated in selection of the appropriate bottle containing thiamine. Accordingly, a circular maze cage 8 inches (20 cm.) high and 3 feet (91 cm.) in diameter was constructed of galvanized iron. It consisted of a central space 12 inches (30 cm.) in diameter, suitable for the feeding cups, and 3 concentric areas, each 4 inches (10 cm.) wide. Rats passed from the central area to the next adjacent concentric area, and thence to successive concentric areas, through one of two circular openings only slightly larger than the body of the animal. The floor area made of wire mesh, 3 to the inch, comprised 7.1 square feet (6600 sq. cm.). Ten rats were housed in the cage. The water-soluble vitamins were provided in amber bottles attached to the cage at places inconvenient for the rat to approach. In this manner, it would seem that all possibility of chance, in selecting the vitamins, was eliminated. The fractions which were considered most essential were provided in places least accessible.

Male rats weighing from 70 to 85 gm. were selected from our breeding colony. The purified diet used was made up as follows: sucrose, 76 parts; vitamin-free casein, 18 parts; corn oil, 2 parts; commercial salt mixture,* 4 parts. Cod-liver oil was given frequently during the experiment. Each gram of the diet contained 3.94 calories, of which 77.1% were derived from carbohydrate, 18.3% from protein and 4.6% from fat.

The fractions of vitamin B provided the animals were thiamine, riboflavin, pyridoxine, calcium pantothenate, niacin and choline chloride. These vitamins were graciously supplied by Merck & Co., and I wish to acknowledge my appreciation of their continued interest in my study. The concentrations of these fractions were so arranged in the various bottles that each cc. of solution contained respectively 100 μg. of thiamine, 200 μg. of riboflavin, 100 μg. of pyridoxine, 200 μg. of calcium pantothenate, 1 mg. of niacin and 10 mg. of choline chloride. In addition to these 6 bottles, 2 bottles containing distilled water were fixed to the cage. The solutions were made up every 3 days. Volumes in cc. consumed from each bottle were measured daily. Food intake was determined daily.

Rats were placed in the cage for 1 week before promin therapy was instituted. The growth of the animals, their food and vitamin intake were recorded during this initial period. Beginning on the 1st day of the 2d week and for each day thereafter for 3 weeks each rat received 50 mg. of promin by mouth. Weights of the animals were recorded at frequent intervals and their intakes of food and vitamin were recorded daily. Observations were made of the

* Marketed by the Harris Laboratories, Tukahoe, N. Y.

appearance and behavior of these animals during the period of administration of promin. On the 22d day after the beginning of administration of promin the blood of all animals was sampled by cardiac puncture. Determinations of the concentration of promin in the blood were made by Dr. Osterberg of the Section on Clinical Biochemistry. The morphologic studies on the blood included the total number of erythrocytes and leukocytes per c.mm., the volumes of erythrocytes in cubic microns, the grams of hemoglobin per 100 cc. of blood and the percentage of reticulocytes. All animals were killed by lightly etherizing and exsanguinating them.

The data condensed into this report were assembled from 4 groups of animals: 2 test groups and 2 control groups. In addition to those rats housed in the maze cage, 10 rats were subjected to the same experimental restriction and given promin in the same way but instead of receiving their vitamins *ad libitum* they were given by tube daily 1 cc. of a solution containing 100 μg. of thiamine, 200 μg. of riboflavin, 100 μg. of pyridoxine, 200 μg. of calcium pantothenate, 1 mg. of niacin and 10 mg. of choline chloride. The blood of this test group of animals was sampled at the end of the experiment in like manner to that of the other test group of animals partaking freely of the vitamins in the maze cage. Each group of test animals was controlled.

Results. 1. *General Appearance and Activity of the Animals.*—Animals fed this purified high carbohydrate diet and given daily by tube the fractions of vitamin B, as indicated, grew satisfactorily, manifested normal hair patterns and did not show any signs of irritability. In the case of animals fed in a similar manner, but given 50 mg. of promin by mouth, definite irritability developed within 24 hours. They became excited and nervous and often jumped from their cages when the door was opened. A number of them chewed their own tails or paws. In a few days hair began to drop off. Some animals presented extreme degrees of alopecia. Severe cyanosis developed. Their food intake was appreciably reduced from 8 to 10 gm. per day to 3 to 5 gm. per day. Their water intake was greatly increased from 12 to 15 cc. per day to 30 to 35 cc. per day. On continued administration of the drug to the animals, tolerance for it appeared to develop. The food intake gradually increased and the nervousness subsided but the extensive alopecia was not relieved.

Animals which were housed in the maze cage and given the same diet and allowed to partake freely of the vitamins grew well and were indistinguishable in appearance from those controls given the vitamins by tube. When promin was given to these animals partaking freely of the vitamins there were no signs of irritability, alopecia did not develop and cyanosis was far less severe than in animals which received the daily allowance of vitamins by tube.

2. *Body Weight.* All animals grew satisfactorily during the initial 1 week trial period before promin was given. The manner of giving the vitamins, by stomach tube as in one group or freely in available bottles as in the other group, did not have any apparent effect on growth during this 1st week. Gains of 18 to 22 gm. per week were recorded (Fig. 1). However, when promin (50 mg. daily by mouth) was given, loss of weight occurred in those animals given the daily constant amounts of the vitamins. On the other hand, those free to select their own, greatly increased their intake of vitamins and did not sustain any loss of body weight. Their growth curve was parallel to,

although not equal to, that of the controls which did not receive promin (Fig. 1). At the end of the experiment (3 weeks of daily administration of promin) the controls had gained an average of

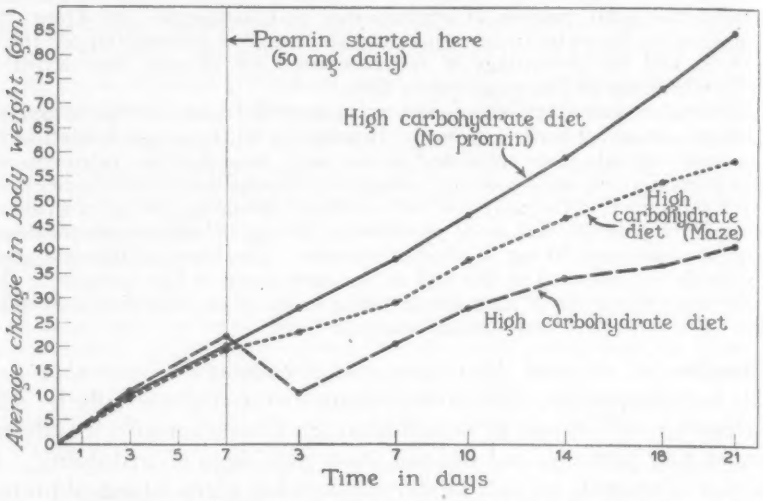

FIG. 1.—Growth of groups of rats fed a purified high carbohydrate diet, with free access to vitamins in the maze or given constant amounts daily by stomach tube. 50 mg. of promin given daily.

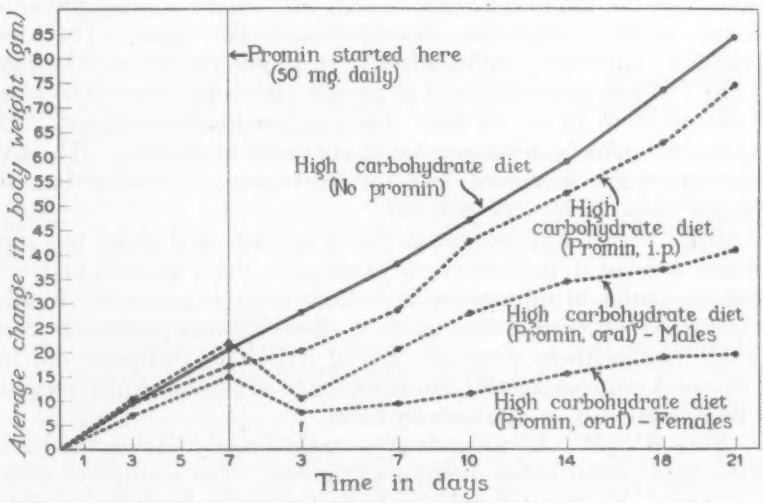

FIG. 2.—Growth of groups of rats fed a purified high carbohydrate diet. Usual vitamin supplements were given to all animals by tube. Growths of females and males when promin was given by mouth, and of males when promin was given intraperitoneally, are shown.

85 gm., those given promin and the vitamins by stomach tube had gained an average of 41 gm. and those given promin with free selection of their vitamins had gained an average of 59 gm.

Female rats, of the same age and weight as males, tolerated the drug less satisfactorily than males and gained but 5 gm. during the 3-week period of administration of promin (Fig. 2). In marked contrast to the toxic effects that oral administration of promin had on growth, I observed that the intraperitoneal administration of the same amounts of the drug for comparable periods had but slight effect on weight (Fig. 2) or appearance of the animal. The characteristic somatic reactions described in an earlier section did not occur in animals given the same amounts of the drug parenterally. It would seem that some of the toxic changes induced by the drug bear some relation to chemical changes which occurred in the gastro-intestinal tract.

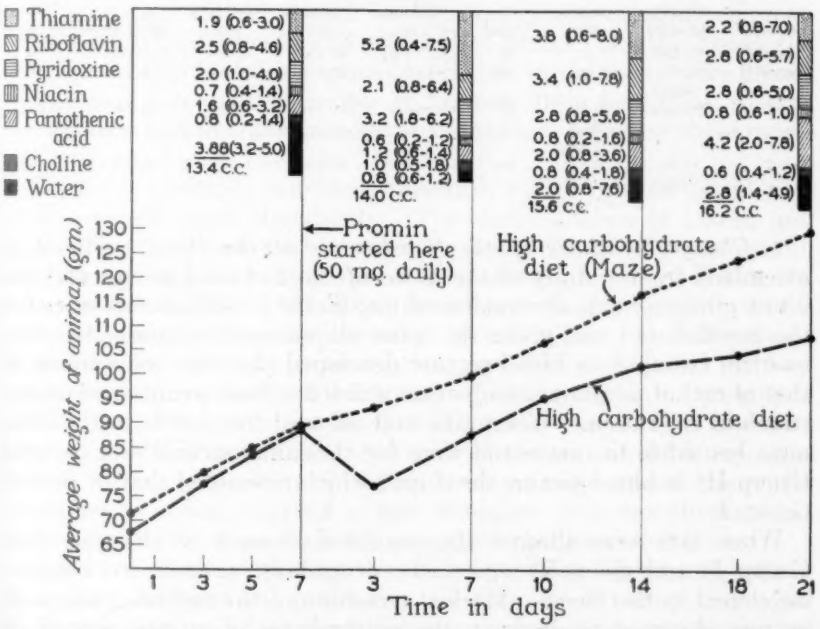

FIG. 3.—Average daily intake in cc. per rat per day of vitamins freely available in bottles attached to the maze. Average intakes per day for 1 week before promin was given, and for 3 weeks of daily administration of promin are shown. The lower lines represent the weights of the rats to which vitamins were freely available in the maze and of those to which constant amounts of vitamins were given.

3. *The Vitamin Consumption per Rat per Day.* The intakes per rat per day of the various vitamins during the week before promin was given, and during the 3 weeks of administration of promin, are shown graphically in Figure 3. These intakes were recorded in cc. Conversion to micrograms is accomplished readily. Although amounts taken were determined daily, only the average daily consumption for each week was plotted. The initial reaction of the animal to promin was to drink larger portions from the bottles containing certain of the vitamins. On some days, an average of 6 to 7 cc. of solutions containing these fractions was taken by each rat. Portions taken from water

bottles, placed conveniently near the food cups, were reduced greatly after administration of promin was started. The amounts of the vitamin preparations taken varied daily. Some days the thiamine intake exceeded that of either riboflavin or pyridoxine. On other days the reverse was true. In any event, either the larger amounts freely taken or the proportions taken by these rats were apparently sufficient to modify the effects of the drug so as to mitigate considerably the toxic changes observed in the rats given the usual daily allowance of these vitamins together with the same amount of promin.

TABLE 1.—SUMMARY OF BLOOD DATA

Group	B-vitamins provided	Amount of promin given	Animals	Erythrocytes (millions per c.mm.)	Volumes in c.micra	Hemoglobin (gm. per 100 cc. of blood)	Reticulocytes (% of erythrocytes)	Blood promin (mg. per 100 cc. of blood)
Control I	By tube	0	10	8.02±0.07	58.1±0.7	13.5±0.2	5.7±0.5	0
Control II	Ad lib. (Maze)	0	10	8.04±0.1	58.4±0.6	12.8±0.2	3.3±0.3	0
Test 1	By tube	50 mg. daily (21 days)	10	3.63±0.3	104.7±2.8	10.3±0.3	58.4±2.3	8.4±0.7
Test 2	Ad lib. (Maze)	50 mg. daily (21 days)	20	5.65±0.1	89.9±1.3	11.4±0.3	25.0±1.7	4.4±0.3

4. *Changes of Some of the Constituents of the Blood.* The data assembled from a study of the blood of the 2 control groups and the 2 test groups of rats are condensed into Table 1. When rats were fed the purified diet and given the usual allowance of vitamins by tube (control Group I), a blood picture developed that was comparable to that of rats of similar age and strain which had been maintained on our standard rat ration. When rats were allowed free access to the vitamins housed in the maze and were fed the same purified diet (control Group II), a blood picture developed which resembled that of control Group I.

When rats were allowed the restricted amount of vitamins (test Group I) and given 50 mg. of the drug daily, pronounced changes developed in the blood. Marked crenation of the erythrocytes, such as was observed to occur in the erythrocytes of guinea pigs given promin, was seen in coverslip preparations of fresh blood from these rats. The blood was very dark. The total erythrocyte count, per c.mm. of blood, ranged from 3,250,000 to 4,800,000. These levels were in marked contrast to the average tabulation of 8,020,000 cells recorded for the control group. Erythrocyte volumes ranged from 87.5 to 126.1 c.micra. Hemoglobin values, in grams per 100 cc. of blood, ranged from 7.6 to 12.4; and the reticulocytes, in percentage of the total number of erythrocytes, ranged from 47.1 to 72.2. The means, together with their probable errors, are set forth in Table 1. The anemia was hypochromic and had some of the features of hemolytic anemia.

The blood sampled from the hearts of rats which lived in the maze cage and had consumed large amounts of the vitamins during the period of administration of promin (test Group II) was considerably better than that in test Group I. There was far less destruction of

erythrocytes. The blood was dark, but less so than in test Group I. Crenated cells in fresh preparations were seen only occasionally. The total number of erythrocytes per c.mm. of blood was 2,000,000 higher and the degree of macrocytosis was correspondingly less. The percentage of reticulocytes, although high, was less than half that encountered in the other test group. The hemoglobin levels, however, were not statistically dissimilar. The report on the promine content of the blood, recorded in mg. per 100 cc. of blood (Table 1), showed that animals, given comparable amounts of the drug by mouth, had a lowered blood level when they partook freely of the vitamins.

Comment. These experiments confirm the extensive studies of Richter and his colleagues[13–17] that when rats are given the opportunity for choice, they will select such foods, minerals and vitamins, as prove essential for their growth and physiologic fitness. In this study the selection of the vitamins was made difficult, in that they were placed in positions not easily accessible and remote from food cups; so that the animals had to travel considerable distances to secure these essential nutrients.

Of the 6 vitamins provided, thiamine, riboflavin and pyridoxine were selected most abundantly. The daily intakes of niacin and choline were not increased perceptibly during the 21-day test period. The requirement for pantothenic acid remained unchanged during the first 2 weeks of the test, but during the 3d week the average daily intake of this vitamin significantly increased. It will be noted that the volume of water taken from the water bottles, purposely placed near the food cups, was reduced during the 1st week of administration of promin to a fifth of that taken during the preceding trial week. It is of course obvious that water was taken with all of the water-soluble fractions but it was an interesting fact that these animals passed the water container to obtain solutions of the vitamins. It seems obvious that some appetite for these fractions prompted the search for them.

A survey of the data suggests that, by taking added amounts of thiamine, riboflavin and pyridoxine, the rats of test Group II avoided the immediate loss of weight which occurred when the usual amounts were given. Their growth curve was not quite equal to that of the control group. Further, the extensive patterns of alopecia which characterized prominized rats that received constant amounts of fractions of vitamin B did not develop in rats partaking freely of these 3 vitamins. The extent of cyanosis, however, the dark color of the blood and the enlarged spleens, all characteristic of reactions to promin, were only slightly improved in the animals taking the increased amounts of vitamins. On the other hand, the destruction of blood was less. All data assembled from our study of the erythrocytes, including crenation, total numbers of erythrocytes, cell volumes and percentages of reticulocytes, indicate that by freely taking those vitamins the rats attained a significant improvement of the blood picture.

The apparent thirst or craving for thiamine particularly, indicates perhaps that in the presence of promin a deficiency of thiamine develops. The hyperexcitability and hyperesthesia of these animals, the

posterior paralysis observed in guinea pigs, and the anorexia and ataxia in rats are symptoms which may suggest such a deficiency. The syndrome is somewhat like that described in young foxes wherein spastic paralysis and death were observed to follow, within 48 to 72 hours, the eating of a diet containing uncooked fish. The addition of large amounts of thiamine to the diet prevented the disease and it was concluded that some constituent of raw fish had the capacity to inactivate thiamine.[5,7,22]

A neutralizing power on the bacteriostatic effect of sulfanilamide has been attributed to p-aminobenzoic acid.[20,21] This was explained as due to some competition in the gastro-intestinal tract for essential enzymes. I have observed that yeast will afford some protection against the toxic action of promin. Since yeast is rich in p-aminobenzoic acid, as well as in other vitamins, it may be that some decrease in the synthesis of the essential enzymes may occur in prominized animals.

Changes of the rate of growth of rats given sulfaguanidine or succinyl-sulfathiazole were thought to be due to changes of the production of the essential growth factors in the gastro-intestinal tract.[2,11,12,19] Liver extract, yeast and p-aminobenzoic acid neutralized the effect of sulfaguanidine. Succinyl-sulfathiazole, which changed prothrombin levels as well as reduced growth rates, was antagonized by liver extracts but not by p-aminobenzoic acid.[20]

These drugs produced agranulocytosis, leukopenia and aplasia of bone marrow. They regularly caused lesions of blood-vessels and voluntary muscles, and often lesions of the heart and liver, to develop. The blood dyscrasia was largely prevented by giving whole dried liver or certain liver extracts. Furthermore the dermatitis which developed when either of these two drugs was given may be prevented or successfully treated with crystalline biotin.[1,3,4,19] Studies in this laboratory, as yet unreported, show that whole liver or yeast, but not liver extract, considerably mitigated the toxic changes induced by promin.

Summary and Conclusions. A study of the relation of vitamin B to the toxicity of promin, as tested by the self-selection method, is reported. Young male white rats, given orally 50 mg. of promin daily, were allowed to take at will such fractions of the B-complex as they desired. The experiment was continued for 28 days: 7 days without promin and 21 with promin. The conclusions reached were as follows:

1. When rats were allowed to take such vitamins as they desired, the intakes of thiamine, riboflavin and pyridoxine were greatly increased after the oral administration of promin. The amounts taken were often increased sixfold over the amounts considered essential for normal nutrition.

2. In the presence of these added vitamins the syndrome characteristic of reactions to promin did not appear. Hyperesthesia, hyperirritability, anorexia, alopecia and transient loss of weight did not develop.

3. Weight curves parallel to, although not equal to, those plotted for control animals were described for animals taking larger amounts of vitamins.

4. Blood values, including the total number of erythrocytes per c.mm of blood, volumes of erythrocytes and percentages of reticulocytes were all improved significantly in animals which consumed larger amounts of the fractions, over those which received comparable amounts of the drug but were allowed smaller amounts of the vitamins.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT

VII. Blood Pyruvate and Lactate–Pyruvate Ratio Following the Ingestion of Glucose in Experimental Deficiency*

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In a previous study of experimentally induced deficiency of the B vitamins[5] in a human subject, an abnormal accumulation of blood pyruvic and blood lactic acid was observed late in the deficiency following the ingestion of glucose. The concentration of these substances

* Sponsored by a fund provided by Mrs. Arthur W. Thompson.

was reduced after the administration of thiamine. Since then Bueding and his associates,[2,3,19] employing a more sensitive pyruvate method, have shown that in patients with clinical evidence of thiamine deficiency a decrease in the rate of removal of pyruvic acid from the blood occurs during the fasting, resting state as well as after the feeding of glucose. More recently Williams *et al.*[17,18] have presented evidence of an impaired breakdown of this acid late in the deficiency of some of their human subjects.

As a result of these observations, a tendency to accept an increased concentration of blood pyruvic acid as diagnostic of early thiamine deficiency has developed. The increase in the pyruvic acid values, however, always occurred in late deficiency, and in the cases of Bueding and associates was associated with clinical conditions where factors other than a vitamin deficiency undoubtedly play a rôle. Before changes in blood pyruvic acid can be accepted as diagnostic of a lack of thiamine, they should be observed consistently in early experimentally induced deficiency, in which other complicating factors which might alter the result, such as variation in physical activity, food consumption and other vitamin deficiencies, can be eliminated.

Accordingly, the present studies were undertaken on 5 women living under carefully controlled conditions of diet and environment. The number of individuals who could be so studied was necessarily limited by the conditions of the experiment. It is our belief, however, that results obtained in this way can be accepted with greater confidence than observations made on a larger number of persons living under less well controlled conditions.

The importance of determining quantitatively both the lactate and the pyruvate was suggested by Stotz and Bessey.[16] They found that in the thiamine deficient pigeon the ratio of lactate to pyruvate, normally constant, was disturbed by an excessively increased concentration of pyruvic acid. Their reports suggested that the simultaneous estimation of both metabolites in the course of a glucose tolerance test might disclose small variations in these substances not detectable by analyses of one or the other separately.

Methods of Study. The studies were carried out in a ward of the Thompson Vitamin Clinic* under the controlled conditions described in an earlier paper in this series[7] where the food, the fluid intake and the physical activity of each subject were rigidly standardized and maintained constant throughout the period of experimental observation. The diet, as described elsewhere,[6] was calculated for each individual so as to contain approximately one-half of the theoretical requirement for thiamine, the other B factors being correspondingly reduced. This type of diet was used because deficiencies of the separate members of the B complex are not likely to be encountered spontaneously in the human being and because the influence of added quantities of other members of the B complex on the utilization of thiamine is not yet well known. The diet supplied adequate quantities of all the other known food factors. Each subject received the diet in constant daily amounts throughout the total period of study. During the initial phase of the experiment the diet was rendered adequate in the B vitamins by a supplement which provided approximately 3 times each individual's minimal requirement for thiamine, riboflavin, niacin,

* Formerly functioning in the Philadelphia General Hospital, but now closed.

pyridoxine and pantothenic acid.* This was designated as "Diet A." Following this first period, the supplement was withdrawn and the subjects subsisted on the basal diet alone: "Diet B." Later, thiamine, 35 mg. daily, was added to the diet, which was then termed "Diet C."

The subjects, women without complicating disease or preëxisting deficiency, served voluntarily. All of them had been residents in the Vitamin Ward for a considerable time prior to beginning the present study and also had served as subjects for other studies of deficiency of the B vitamins to be reported elsewhere.

Three subjects (B. A., C. S. and A. M.) were tested after 3 to 5 days on Diet A and again after a short period, 2 to 9 days, on Diet B. None showed any evidence of clinical deficiency at the time of testing. Two subjects (M. B., F. S.) were tested after 1 to 7 days on Diet A and again after 48 to 50 days respectively on Diet B. At the time of testing on this regimen, both subjects showed early clinical evidence of deficiency. Subject F. S. was then tested following 13 days on Diet C at which time the clinical symptoms had improved.

The chemical methods have been presented previously by one of us.[11,12] Lactic acid analyses were done by the Barker-Summerson modification[1] of the Miller-Muntz method.[14] Blood pyruvate and lactate levels were determined with the patients fasting and at rest and also following the oral administration of glucose, according to the procedure already described.[12]

Results and Discussion. In the control experiments (Diet A) all subjects showed normal pyruvate levels (Table 1) under basal conditions and temporary increases following the feeding of glucose. The response of pyruvate was similar to that previously described in normal subjects.[11]

TABLE 1.—BLOOD PYRUVIC ACID, FASTING AND FOLLOWING THE INGESTION OF GLUCOSE ON AN ADEQUATE DIETARY REGIMEN (DIET A)

		Time after ingestion of glucose				
		Fasting	0.5 hr.	1 hr.	2 hrs.	3 hrs.
Subject	Time on diet (days)	Mg. pyruvic acid per 100 cc. blood				
F. S.	1	0.77	0.87	0.98	0.99	0.77
C. S.	3	0.59	0.66	0.74	0.83	0.70
M. B.	7	0.75	0.76	1.12	1.13	0.84
Average:		0.70	0.83	0.95	0.98	0.77

TABLE 2.—BLOOD PYRUVIC ACID, FASTING AND FOLLOWING THE INGESTION OF GLUCOSE WHILE TAKING A DIET DEFICIENT IN THE B VITAMINS (DIET B) FOR A TIME INSUFFICIENT TO PRODUCE CLINICAL MANIFESTATIONS OF DEFICIENCY

		Time after ingestion of glucose				
		Fasting	0.5 hr.	1 hr.	2 hrs.	3 hrs.
Subject	Time on diet (days)	Mg. pyruvic acid per 100 cc. blood				
B. A.	2	0.84	0.84	1.17	1.08	0.96
C. S.	7	0.95	1.39	1.28	1.17	0.96
A. M.	9	1.07	1.16	1.53	1.62	1.03
Average:		0.95	1.13	1.33	1.25	0.98

When the subjects had consumed the basal diet (Diet B) for a brief period, insufficient to produce clinical manifestations of thiamine deficiency, some increase in the height of the pyruvic acid curve occurred following the ingestion of glucose (Table 2). This was due to

* Kindly supplied as "Pentaplex" by Smith, Kline & French Laboratories, Philadelphia.

the high initial as well as subsequent pyruvate values for both Subjects C. S. and A. M. However, the shape of the curve in each instance was not abnormal and values returned to the fasting level at the end of 3 hours. Thus, as would be expected, no change in rate of removal of pyruvic acid was detectable after 2 to 9 days on the deficient diet.

TABLE 3.—DAILY INTAKE OF THIAMINE (DIET B) AND AVERAGE DAILY URINARY EXCRETION OF THIAMINE AT TIME OF TEST

Subject	Days on Diet B	Daily intake of thiamine (μg.)	Average daily urinary thiamine (μg.)
B. A.	2	274	67
C. S.	7	262	61
A. M.	9	262	
M. B.	48	279	12
F. S.	50	214	11

After 48 to 50 days on the basal diet (Diet B) definite evidence of deficiency was present in subjects M. B. and F. S. Both showed the typical[4,18] early symptoms of increased irritability and apprehension, together with gastro-intestinal complaints and shifting pains particularly in the lower extremities. Average daily urinary excretion of thiamine was commensurate with intake (Table 3) and cannot, as discussed elsewhere,[7] be regarded as a measure of the degree of deficiency. In both these subjects, however, a delayed excretion of a test dose of thiamine occurred, a response that correlates fairly well with the onset of clinical deficiency.[9] In both instances the manifestations of deficiency were those which, unless the subjects had been under careful supervision and unless it had been known that deficiency of the B vitamins was the only operating factor, might have been missed. The deficiency, therefore, was of the "sub-clinical type" for which a diagnostic test is eagerly sought. The pyruvic acid values in these subjects (Table 4) did not differ in any significant way from the normal or from those after a short period on the basal diet. The fasting values were within normal limits, and the shape of the curves after glucose was, likewise, entirely normal. The 3d hour value in subject M. B. was slightly elevated but not to a degree to be regarded as significant. Administration of thiamine (35 mg.) for 13 days to subject F. S. produced no change in pyruvic acid values although clinically she was much improved.*

It is greatly regretted that owing to the exigencies of the war, it was impossible to prolong the experiment further, in order to see at what point in the development of deficiency, abnormal values would have first become evident. From our own experience[5] and that of Williams and his associates,[18] however, it seems fairly certain that such changes develop only when clinical deficiency is well established. In view of these facts it is most unlikely that alterations in blood pyruvic acid, either fasting or after the administration of glucose, can serve as a diagnostic test for early deficiency. Furthermore, given abnormal values for pyruvic acid, great caution should be used in attributing

* Blood pyruvic acid values were: fasting, 0.73; ½ hour, 0.86; 1 hour, 1.17; 2 hours, 0.94; 3 hours, 0.81.

such changes to deficiency of the B vitamins in the absence of definite clinical evidence of deficiency since many other factors[8,13] are known to alter blood pyruvic acid concentration. Blood lactic acid values paralled the pyruvic acid, resulting in a constant lactate-pyruvate ratio (Table 5). Thus, determination of this ratio added nothing to the sensitivity of the test as observed in thiamine deficient pigeons.[16]

TABLE 4.—BLOOD PYRUVIC ACID, FASTING AND FOLLOWING THE INGESTION OF GLUCOSE WHILE TAKING A DIET DEFICIENT IN THE B VITAMINS (DIET B) FOR A TIME SUFFICIENT TO PRODUCE EARLY SYMPTOMS OF DEFICIENCY

Subject	Time on diet (days)	Time after ingestion of glucose: Fasting	0.5 hr.	1 hr.	2 hrs.	3 hrs.
		Mg. pyruvic acid per 100 cc. blood				
M. B.	48	0.87	1.04	1.16	1.03	1.07
F. S.	50	0.91	0.98	1.19	1.33	0.99
Average:		0.89	1.01	1.18	1.18	1.03

TABLE 5.—BLOOD LACTATE–PYRUVATE RATIO, FASTING AND FOLLOWING THE INGESTION OF GLUCOSE IN THE DIFFERENT EXPERIMENTAL PERIODS

Subject	Time after ingestion of glucose: Fasting	0.5 hr.	1 hr.	2 hrs.	3 hrs.
Diet A:					
F. S.	7.5	7.7	9.4	9.6	8.6
C. S.	10.2	10.2	10.1	10.0	9.3
M. B.	9.9	9.6	9.0	9.4	10.4
Diet B (2–9 days):					
B. A.	9.0	9.5	9.8	10.0	10.6
C. S.	8.0	9.3	9.8	8.5	8.0
A. M.	8.2	8.9	9.6	9.6	9.5
Diet B (48–50 days):					
M. B.	8.4	9.1	9.2	11.1	10.7
F. S.	7.9	8.3	9.4	9.9	8.7
Diet C:					
F. S.	8.8	9.3	9.7	10.7	9.1

Summary. Blood pyruvic acid values as well as the blood lactate to pyruvate ratio, fasting and following the administration of glucose, did not differ from the normal in 5 subjects living under carefully controlled conditions and ingesting a diet deficient only in the B vitamins, even though manifestations of "sub-clinical" deficiency became evident in 2 of them.

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PROGRESS
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SURGERY

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THE RÔLE OF NUTRITION IN PREOPERATIVE AND POSTOPERATIVE CARE

A Review

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Although treatises on therapeutics refer many times to increasing the nutritional state and general resistance of patients, the true significance of this often repeated phrase is probably not realized by many physicians and surgeons. No one need impress upon the medical profession the importance of nutrition; it is evident in everyday practice. We need to know more about methods of reëstablishing and maintaining the nutritional status of patients. The science of nutrition has progressed rapidly in the past 25 years. It has been said that practicing physicians have not kept pace with the increased knowledge of nutrition.

That nutritional deficiencies do decrease resistance to generalized infections has been demonstrated by E. C. Robertson.[43] She has shown that deficiencies of thiamin chloride, the B complex, vitamin D, vitamin C, protein or minerals reduce the ability of rats to survive a generalized infection. Undoubtedly, further investigation will augment this list. It is apparent that the diets previously regarded as adequate do not offer an optimum amount of nutritional elements. This fact is attested by the recent encouragement of bakers by The Food and Drug Administration to enrich baking products with added vitamins. Campbell and Sherman[10] have shown by animal experiments that, starting with a diet already considered adequate, the feeding of additional food elements will increase the rate of growth, will produce a larger adult size with earlier maturity, and will prolong the period of adult life.

A fundamental understanding of the problems of nutrition and an application of that knowledge will reduce operative morbidity and mortality. Nutritional problems in surgery are numerous. It is not possible to dis-

* Now on Active Service in the Armed Forces.

cuss in a few pages all of these problems. In the following paragraphs the items of nutrition which most concern the surgeon are briefly discussed in the light of their influence upon surgical patients. Included also are limited discussions of the nutritional treatment of some specific surgical conditions.

Protein. Protein is necessary for growth and repair of tissues, for formation of secretions, both internal and external, for the transport of fat, and at times for the production of energy. The reserve store of protein in the adult body averages 4.5 pounds.[8a] In the hydrated state this protein may represent as much as 26 pounds, a considerable portion of the body weight. If this protein were the only store called upon to supply energy during a period of starvation, these 26 pounds of hydrated protein could supply the basal caloric requirements of the average adult for only 5 days. Most common chronic protein deficiencies are caused by (1) inability to ingest food due to pain or vomiting, (2) inability to assimilate food due to intrinsic gut changes, (3) a diet prescribed by one unfamiliar with the problems of nutrition, and (4) inability to obtain food for economic reasons. The body stores of protein are reflected in the level of the serum protein. The serum protein is, therefore, our measuring stick of the body store of protein. Obviously, in acute hypoproteinemia, as caused by burns, hemorrhage, marked intestinal distention, and intestinal obstruction, the serum protein level is not an accurate index of the body reserve of protein.

Hypoproteinemia causes edema, poor wound healing, retarded bone healing, a decreased resistance to generalized infection, a delay in gastro-intestinal motility, and it may be the cause of failure of function of surgical gastro-intestinal stomata. The surgeon should be greatly concerned when his patient has a low serum protein level.

Clinical edema, which represents an increase of at least 10% of weight by edema fluid, usually appears when the serum protein level falls below 5.5 gm. %; however, *incipient edema* appears as soon as the serum protein level falls below 7 gm. %. One should not delay the treatment of hypoproteinemia until clinical edema appears, for, long before this stage of edema is reached, the adverse effects of hypoproteinemia and *incipient edema* are at work.

Thompson, Ravdin and Frank[50] were the first to demonstrate that hypoproteinemia caused wound dehiscence. Hartzell and Winfield[18] found in a study of wound separation that all of the patients had a deficiency of protein or vitamin C or both. The retardation of the healing of fractures in the presence of hypoproteinemia was noted by Rhoads.[41] Following the suggestion of Jones and Eaton,[23] Barden, Ravdin and Frazier[4] first showed that hypoproteinemia could cause a failure of function of an otherwise mechanically perfect gastro-enterostomy stoma. Delay in gastric emptying and the delay in the stomach-to-cecum time in the presence of hypoproteinemia, and the return of gastro-intestinal motility to normal following the restoration of the serum protein to normal levels have been reported by Mecray, Barden and Ravdin[28] and Barden *et al.*[5]

Acute hypoproteinemia is overcome by immediate replacements of large quantities of blood and plasma. The magnitude of the problem of treating chronic hypoproteinemia becomes apparent when one realizes that according to Elman's calculations[12] 375 gm. of protein are required each day for a period of 10 days in order to elevate a serum protein level from 5 to 7 gm. %. Sachar and Elman[44] have found that for every gram of protein deposited in the serum 30 gm. are deposited in the body in general.

Obviously, the easiest and best way of overcoming hypoproteinemia is by means of a high protein, high caloric diet. Such a diet might well be recommended preoperatively just as soon as a hospital appointment is made for an elective operation. Patients who cannot ingest or assimilate food must receive protein by some other route. Ravdin has demonstrated the effectiveness of feedings by means of a gastric or jejunal tube.[46] Plasma has been shown by Whipple[53] to be the most efficiently utilized protein in the treatment of hypoproteinemia. Protein hydrolysates may be administered by gastric or jejunal tube[46] and occasionally by the rectal route. Mixtures of amino acids are now being prepared commercially for intravenous use. It is often possible to maintain a normal adult in nitrogen balance with these preparations. Although rapid strides are being made in the preparation of amino acids, it has not yet been possible to maintain chronically ill patients in nitrogen balance.[29]

The Miller-Abbott tube[1] has made it possible to restore nutrition prior to operation in the presence of partial or complete intestinal obstruction. A modification of the Miller-Abbott tube, the Abbott-Rawson tube,[2] has made it possible to maintain nutrition in the immediate postoperative period following operations of the stomach and duodenum. The advantages of maintaining nutrition during this period have been emphasized by Ravdin, Stengel, Prushankin,[38] and Mulholland.[29] If an Abbott-Rawson tube has not been used it is occasionally necessary to perform a jejunostomy in order to restore the nutritional status of certain patients.

Carbohydrate. Carbohydrate and fat together primarily furnish energy to the body. Carbohydrate has a protein-sparing action. During World War I large groups of people in Central Europe who received insufficient food were found to have anemia and edema secondary to hypoproteinemia. Yet it was observed that when an adequate amount of carbohydrate was added to their diet the protein deficiency symptoms disappeared entirely.[8a] When present in amounts in excess of the caloric requirements, carbohydrate may be stored as fat.[35] Carbohydrate is of the utmost importance to the surgeon because it is easily prepared and administered by the intravenous route as glucose solution during the periods when a patient is unable to take nourishment by mouth. Glucose, when administered intravenously, is 95 to 98% utilized according to Winslow.[54]

Fat. Fats yield almost twice as much energy in the form of heat as does carbohydrate. Fat alone does not have the same protein-sparing action that carbohydrate exhibits, but almost any mixture of fat and carbohydrate will spare protein to the same extent as carbohydrate alone. Myers and Blumberg,[30] Narat,[31] and others have prepared emulsified fats for intravenous use. An excessive store of fat increases operative mortality. Fatty tissues heal poorly and are prone to develop hematomata, serum collections, and infections.[52] Fat has indirectly an adverse effect upon the liver. A high liver lipid content predisposes to liver injury, as has been shown in the experimental animal.[16]

Fluids. Water is an important nutritional item. Man cannot exist for long without it. Adequate hydration and its relation to surgery was recognized many years ago. Maintenance of the body fluid level, both intracellular and extracellular, is of the utmost importance to the surgical patient. Recent literature contains many excellent articles on the subject of fluid balance.[11,25] Fluid intake should be so adjusted that the urinary output is maintained between 1000 and 1500 cc. daily.

When clinical signs of dehydration are present, Maddock and Coller[26] have shown that there is dehydration equivalent to at least 6% of the

body weight. A dehydrated patient should receive 6% of the body weight in fluid in addition to his normal fluid requirement. In addition to its other effects, dehydration also retards wound healing.[9]

Sodium Chloride. Along with the understanding of fluid balance we have gained a knowledge of the importance of electrolyte balance. Water balance cannot be separated from salt metabolism because the retention of water is largely dependent upon the amount of sodium in the body tissues. In order to compensate for salt losses of the skin and feces, to facilitate acid base adjustments, and to maintain the body fluid volume, the daily salt intake should be from 5 to 10 gm.[6] Any excessive loss of electrolyte must be replaced with additional salt and fluid. Marked lethargy, dulling of sense, taste, and mentality, muscular twitching, loss of elasticity of the skin, acidosis or alkalosis are signs of hypochloremia. Calculated doses of sodium chloride as suggested by Power *et al.*[36] are used to overcome chloride deficits.

Vitamins in Surgery. To produce preoperatively and postoperatively a more nearly normal physiologic state in the surgical patient, the administration of vitamins as advocated by Vorhaus[51] is often essential. Vitamins are essential for normal physiologic processes in the body. A deficiency of vitamins may cause serious physiologic disturbances long before the gross pathologic changes characteristic of avitaminoses become apparent.[47] The members of the B complex act as enzymes and coenzymes for carbohydrate metabolism in the body and as such they are being constantly destroyed.[15,35,49] Sydenstricker[47] has noted that a critically ill patient, receiving intravenous glucose as his only caloric intake, may develop signs of thiamin chloride deficiency in as short a time as 3 or 4 days. Similarly a nicotinic acid deficiency may occur with the development of glossitis and mental confusion. Symptoms of both thiamin and nicotinic acid deficiency disappear with the administration of these vitamins according to Sydenstricker.[47] Frazier and Ravdin[13] have noted that hyperthyroid patients following the administration of thiamin, show greater increase in weight and appetite, and a greater fall in heart rate than patients who received no additional vitamins.

Vitamin A. Vitamin A itself probably does not materially affect the course of surgical patients. That vitamin A is of value in reducing the incidence of respiratory infections and that it is of value in the stimulation of the healing of surgical wounds has not been generally accepted.[45]

Vitamin C. It has been demonstrated by many investigators that vitamin C is essential to normal wound healing.[19,48,55] Vitamin C is necessary for maturation of precollagen to the collagen of fibrous tissue. From 27 to 44% of apparently normal people have vitamin C plasma levels below the lower limit of the normal accepted vitamin C range.[20,42] Patients with certain chronic surgical diseases have, on the average, vitamin C levels which are well below the lower normal limit of plasma vitamin C level.[7,8,21,56] A definite fall in the plasma vitamin C level following operative procedures has been noted by Bartlett *et al.*[7]

Vitamin D. The fat-soluble vitamin D is important in the body metabolism of calcium and phosphorus. In its absence more calcium is lost from the body than is furnished by the diet. Vitamin D is necessary for normal bone growth and bone repair.

Vitamin K. Vitamin K is a group of specific substances associated with the maintenance of a normal blood clotting mechanism. Deficiencies predispose to hemorrhage. It is now possible to restore the blood prothrombin time to normal in the majority of patients within 72 hours. The

comparative activities of the more commonly used antihemorrhagic compounds have been listed by Starr.[45] Treatment of resistant cases of prothrombin deficiency has been adequately discussed by Rhoads.[40] Destruction of prothrombin occurs constantly in the body[3] and, therefore, when the pathologic state which caused the deficiency remains unchanged, repeated intravenous injections or oral administration (together with bile salts) is necessary until the clinical condition improves.

Diet in Biliary Tract Diseases. The preoperative preparation of patients with liver disease is of the utmost importance, especially in those patients with a history of prolonged or intermittent jaundice. The danger in biliary tract surgery lies mainly in the fact that operation adds further damage to an already impaired liver.

Opie and Alford[32] in 1914 reported on the beneficial effect of a high carbohydrate diet in protecting the liver from chloroform necrosis. For a number of years following their report, carbohydrate by mouth and by vein was used to treat liver diseases and to protect the liver from further damage. More recently Goldschmidt, Vars and Ravdin[16] have shown that the degree of liver injury is dependent upon the amount of fat present in the liver, no correlation being noted between the level of liver glycogen and the degree of liver damage. A diet containing 20% of protein, 75% of carbohydrate and 5% of fat has proved its superiority over other types of commonly used diets in preparing the liver for minimal damage by decreasing the amount of liver fat in the experience of Ravdin *et al.*[39] and Johnson *et al.*[22]

Nutrition in Gastric and Duodenal Surgery. Probably no major surgical procedure requires as meticulous and thorough preparation and aftercare as do operations of the stomach and duodenum. Factors to be considered are (1) fluid requirements, (2) electrolytic requirements, (3) caloric intake, (4) vitamin intake, (5) protein intake, and (6) the mechanical difficulties. All but one of these 6 factors are problems of nutrition. Care of these patients has been described, among others, by Ravdin,[37] R. Graham,[17] and Kiefer.[24] The advent of the Abbott-Rawson tube[2] has greatly facilitated the postoperative treatment of these patients. Exteriorization of the Abbott-Rawson tube through the abdominal wall, as suggested by Bisgard,[9a] appears to have advantages. Failure of function of a newly formed stoma may be due to the edema which accompanies hypoproteinemia, as has been pointed out by Mecray, Barden and Ravdin.[28] When feedings are begun by mouth, fatty foods are to be avoided, because Pendergrass *et al.*[33] have demonstrated a delay in gastric emptying time following ingestion of fat.

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OPHTHALMOLOGY

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SENILE CHANGES IN THE CHOROID AND RETINA

By H. P. Wagener, M.D.

A review of the so-called senile degenerations of the choroid and retina might be considered to be of no more than academic interest if one adopts the rather hopeless attitude suggested in Zentmayer's[22] statement: "There are of course many other senile changes met with in the eye such as the macular degenerations, but their early detection is not of great importance, as we can do nothing for them." Crisp[6] states: "Senility and death begin at birth, or rather in the early stages of embryonic development. The vascular system, which has so obvious a share in the aging process, is constantly in course of modification, and each step in such modification may logically be considered as a move in the inevitable

march from conception toward death." However, Crisp[6] recognizes the "lack of unanimity in disintegration" in the human organism and states that "the tissues of the eye illustrate beautifully this tendency to unequal aging as between different parts of the body" and that "the extent to which changes commonly regarded as senile are really due to infection or other extraneous influence may often be in doubt." Along these lines, de Schweinitz,[17] in 1925, called attention to the favorable influence upon the early stages of so-called senile macular retinochoroiditis of the elimination of foci of infection, notably in the prostate, bladder and teeth. And even Zentmayer[22] himself stated that "indulgences which in early life are without serious or appreciable injury to the body tissues and functions, in later life either as a result of cumulative action of the toxic agents or of lowered resistance of the tissues, or both, may bring in their train functional impairment or serious organic change." More recently experts in nutrition and nutritional diseases have called attention to the similarity or identity between certain lesions of the eye commonly considered to be "senile" and those due to chronic long-continued avitaminosis or nutritional deficiencies existing from birth or even before birth in the mother. This attitude to the mode of development or rather prevention of at least some of the "senile" changes in the eye is epitomized in the statement of Dr. Katherine Bain[2] that, in order to have well-nourished adults in 1961, babies must be fed properly now. With these ideas in mind, it was thought that a review of some of the more common so-called senile lesions in the retina and choroid and of their histologic background might stimulate their earlier recognition in the chronologically presenile group of individuals in whom they occur not infrequently and in whom perhaps a causative background other than age alone might be more readily discovered than in the truly aged.

In the choroid, according to Duke-Elder,[7] the essential senile changes occur primarily in the blood-vessels and secondarily in the tissues dependent on the choroid for nourishment, the lamina vitrea of the choroid, the pigment epithelium of the retina, and in the retina itself, especially in the macular region. It is rather difficult to determine, at least ophthalmoscopically, the types or instances of choroidal arteriosclerosis which may be said to be dependent on age alone. Histologically, 3 types of choroidal arteriosclerosis may be distinguished. Duke-Elder[7] states that in the senile atherosclerotic type of choroidal arteriosclerosis there is "a deposition of lipoids in the intima associated with fibrous tissue proliferation and followed by hyaline degeneration which may be extensive, sometimes with the formation of large atheromatous plaques. In this senile change the thickening and hyalinization of the adventitia and media may be so marked that it may be difficult to differentiate these structures from the hyalinized connective tissue surrounding the vessels; but there is little narrowing of the lumen or tendency to obliteration." However, he states later that the lumen may be restricted or even obliterated by the hyalinization of the walls "so that the vessel takes on the appearance of a white opaque tube with thick striated walls." There may be an accompanying thickening of the walls of the veins by connective tissue increase. It is possible that the vessels with obliterated lumens belong more strictly to the lesions associated with hypertensive disease which Duke-Elder[7] refers to as the "more arteriosclerotic types" in which "there is connective tissue proliferation of the media with reduplication of the internal elastic lamina so that eventually extreme narrowing or even obliteration of the lumen may follow. The ultimate result may be complete occlusion of

the vessel with advanced hyaline or lipoid degeneration and complete degeneration and disorganization of the cells of its walls." It is probable that endothelial proliferation plays a rôle also in the obliteration of the lumen of the choroidal arteries in hypertensive disease. A third histologic type of choroidal arteriosclerosis is described by Cohen[5] as a replacement of the muscular coat of the arteries by fibrous acellular tissue with some degeneration of the elastic lamina but without actual thickening of the walls or narrowing of the lumen.

From the clinical ophthalmoscopic standpoint it seems possible that the hypertensive or "arteriosclerotic" type is represented by the isolated, apparently obliterated or essentially obliterated choroidal arteries associated with "Siegrist's dots." The clinical interpretation of the scattered patches of choroidal arteriosclerosis seen mainly in elderly individuals but not associated with loss of vision would be much clearer if it was known definitely whether the sclerosis was histologically of the arteriosclerotic or the atherosclerotic type. Cohen's findings suggest that the so-called primary choroidal sclerosis, the principal symptom of which is loss of vision due to secondary degenerative changes in the retina, may have as its histologic basis the fibrosis of the media that he describes. However, on the basis of the histologic findings it is rather difficult to explain the ophthalmoscopic appearance of vascular obliteration to which both Cohen[5] and Duke-Elder[7] refer. The principal types of primary choroidal arteriosclerosis which are observed are the diffuse choroidal sclerosis or atrophy of the choroid (Morton),[13a] the central areolar choroidal atrophy, and the massive peripapillary choroidal sclerosis which is probably an exaggeration or extension of the so-called senile halo. It is of interest that all these types of choroidal sclerosis and atrophy, while they occur most commonly in individuals over 60 years of age, are seen occasionally in the young, and that there seems to be a certain familial incidence.

Considerable confusion exists concerning the clinical interpretative value of choroidal arteriosclerosis with reference to the presence of arteriosclerosis elsewhere in the body, particularly in the brain and in the coronary arteries. By some authorities, choroidal arteriosclerosis is regarded as a constant age change. Thus, Kerschbaumer[12] stated that it was present in 50% of people between the years of 40 and 50, in 75% of those between 50 and 60, and in all over 60 years of age. And Friedenwald[8] concluded that arteriosclerosis in the choroid starts usually at the age of 40 and, as in the spleen, progresses slowly without any direct relationship to general vascular disease. It is one's impression, however, that, though this may be true from the histologic standpoint, yet, from the ophthalmoscopic standpoint, more careful differentiation of the types of visible choroidal arteriosclerosis may yield ultimately some information of value with regard to the diagnosis of arteriosclerosis in other parts of the vascular system.

The visibility of changes in the larger vessels of the choroid depends to a certain extent upon the amount of pigment present normally in the individual choroid and retinal pigment epithelium. Thus, early changes are seen most readily in lightly pigmented eyes. As the sclerosis becomes more advanced, however, secondary changes in the intervascular stroma (degeneration), in the choriocapillaris (sclerosis and atrophy), and in the retinal pigment epithelium (degeneration, depigmentation and atrophy) increase the visibility of the larger choroidal vessels even in the normally heavily pigmented eye. These secondary degenerative changes in the choriocapillaris and in the retinal pigment epithelium give rise to most of

the senile degenerations of the macular choroid and retina which cause loss of central vision in the aged.

The most commonly seen senile change in the choroid is the deposition of hyaline masses in the lamina vitrea of the choroid. These yellowish-white spots have been variously designated as "drusen," colloid bodies, hyaline bodies, and guttate choroiditis or guttate degeneration. When they are small and scattered they cause no disturbance of vision and are considered to be of no significance. When they become larger, and especially when they are massed in the macular region, however, they may cause pressure atrophy of the overlying rods and cones with resultant serious impairment of vision. According to Duke-Elder,[7] such cases were first described by Hutchinson[11] under the name of "symmetrical central choroidoretinal disease occurring in senile persons and later came to be known as Tay's central guttate choroiditis." Recently attention has been called again to the significance of these lesions by Gifford and Cushman,[9] who include Doyne's honeycomb choroiditis among lesions of this type. They prefer the term "central retinopathy due to hyaline deposits of the lamina vitrea." They believe that at least some of the cases of central disk-shaped retinopathy or disciform degeneration of the macula (Kuhnt-Junius)[11b] develop on the basis of hyaline degeneration of the lamina vitrea. These cases have usually been ascribed to arteriosclerosis of the retinal or choroidal vessels. However, according to Gifford and Cushman,[9] Behr[3] "found degenerative changes in the lamina vitrea with a number of vessels growing through it into the choroid. He expressed the belief that the primary cause of the condition was a senile or nutritional defect in the elastic system of the choriocapillaris and lamina vitrea which allowed a transudate to collect beneath the pigment epithelium. From this the connective tissue developed by proliferation of pigment epithelium and growth of new vessels from the choroid." As a result of their investigations of a case presenting a juvenile form of central disciform retinopathy, Gifford and Cushman[9] obtained evidence in support of the location of the primary lesion in the lamina vitrea rather than in the vascular system. They stated that "evidently complete defects in the membrane may not be necessary for the production of the typical condition but only an altered permeability which permits fluid from the choriocapillaris to collect beneath the pigment epithelium. Proliferation of the pigment epithelium seems to result from such a transudation. If vessels from the choroid do not grow into the resulting mass, hemorrhages may be absent from the picture." In this conception of the origin of the lesion, it is probably necessary for the occurrence of hemorrhage, that complete defects exist in the lamina vitrea to allow the growth of vessels from the choriocapillaris into the transudate under the pigment epithelium.

In their cases, Gifford and Cushman[9] did not find more marked evidences of hypertension and generalized arteriosclerosis than the average in the age group affected. Nor were there any marked evidences of retinal arteriolosclerosis. They favor the conception of a senile or presenile degeneration of the lamina vitrea belonging to the so-called abiotrophies of Treacher Collins. Yudkin[21] suggested that deficiencies or disturbances of nutrition in early life might be a factor in the subsequent development of drusen, but Gifford was inclined to disagree with this suggestion. That some factor other than age alone may be involved in the production of these hyaline degenerations is suggested, of course, by their occurrence not infrequently in young people in whom they "may be due to some obscure general or local metabolic disturbance" (Duke-Elder).[7]

In his discussion of Gifford and Cushman's paper, Verhoeff[20] stated his belief that the cause of disciform degeneration of the macula is hemorrhage beneath the pigment epithelium of the retina in the senile form and serous exudation in the same location in the juvenile form. He thinks that senile degeneration of the pigment epithelium is the primary change which predisposes to hemorrhage from the choriocapillaris and that the lamina vitrea is only slightly affected. In the end, this difference of opinion may be only a matter of the extent of visible damage to the lamina vitrea in the sections examined since hyaline changes in the lamina vitrea are supposed to be the product of primary degenerative changes in the pigment epithelium. The senile type of colloid spots, or drusen, it is generally agreed, are due to the deposition of hyaline material in the cuticular layer of the lamina vitrea as a result of metabolic disturbances in the pigment epithelium with excessive secretion of the hyaline substance (Rones).[15] Rones thought that the "degenerative" type of drusen was formed by the actual transformation of degenerated pigment epithelium cells. However, Verhoeff[19] was inclined to think that all forms of drusen were due to the deposition of hyaline material beneath the pigment epithelium.

Another lesion of the macular retina in old people which is presumed to depend on primary damage to the choroidal circulation is the senile macular degeneration of Haab which is stated by Duke-Elder[7] to be "characterized by the presence of degenerative changes, usually punctate in nature, occurring bilaterally, limited to the region of the macula, and due to sclerosis and obliteration of the choriocapillaris in the central area." The ophthalmoscopic findings are limited in the early stages to a mild pigment stippling of the macular retina which appears to be insufficient in amount to account for the loss of vision. Later there is evident decoloration of the fovea due to the sclerosis and atrophy of the underlying choriocapillaris and still later hemorrhages and transudation may occur in the retina and choroid so that the ultimate picture may be essentially indistinguishable from that seen in other forms of choroidal sclerosis and atrophy or even in disciform degeneration of the macula. Correspondingly, the histologic changes in the advanced stages comprise sclerosis and hyaline degeneration in the vessels of the choroid, especially of the choriocapillaris, colloid excrescences of the lamina vitrea, exudation under the pigment epithelium, atrophy and proliferation of the pigment epithelium, and atrophy and disorganization of the deeper layers of the retina with essential destruction of the rods and cones.

Retinitis circinata (circinate retinopathy, or circinate degeneration of the retina) is another lesion which occurs usually in elderly individuals and which is often ascribed to changes in the choroidal circulation. According to Duke-Elder,[7] it was described originally by Hutchinson[11] under the title "symmetrical central choroido-retinal disease occurring in senile persons" and is characterized by "a girdle of bright white spots in the deeper retinal layers around the central area and the development of degenerative changes at the macula." The characteristic white exudation observed ophthalmoscopically is represented histologically by sero-albuminous, hyaline or fatty degenerative changes in the internuclear and internal nuclear layers of the retina. These were considered originally by Amman to be the residuals of hemorrhagic extravasation. But it seems more probable, as noted by Morax[13] and Seefelder,[18] that the exudation is essentially similar in nature to that seen in hypertensive retinopathy and is dependent primarily on impairment of the circulation as the result of arteriosclerosis either in the retina or, as suggested by Seefelder,[18] in the

choroid. In Seefelder's case, there was an associated advanced cystoid degeneration of the macular retina with complete disappearance of the outer layer and the layer of rods and cones. Senile macular degeneration was present also in the other eye of Seefelder's patient.

According to Berens,[4] 4 clinical types of central senile chorioretinitis were described by de Schweinitz.[17] In Type I "the macula may appear darker than normal, it may be delicately mottled or white glistening spots may be seen." In Type II "yellowish white spots in the macula are interspersed with pigment dots and occasionally with hemorrhages." In Type III "a round or slightly oval hole appears in the macula." In Type IV "grayish or greenish heaped exudates, which may resemble tumors and hemorrhages, may be present." It seems probable that Types I, II and IV represent various phases in the progressive development of senile macular degeneration (Haab)[9a] as described previously. Probably Type III belongs more properly in the group of cystoid degenerations of the retina.

It is well known that the senile retina has less luster and gives off fewer light reflexes than that of the child and young adult. Duke-Elder[7] states: "In the aged the retina shows less marked evidences of senility than most tissues. As a whole it becomes less transparent owing largely to an increase in the neuroglial elements, a process which is associated with a parallel tendency to atrophy of the neural elements." In some instances, "the whole thickness of the retina may undergo fibrous transformation and cystic degeneration." This occurs usually in cases in which there is sclerosis and atrophy of the choriocapillaris. Quoting again from Duke-Elder,[7] "Cystic or cystoid degeneration of the retina is properly a passive degenerative process wherein gaps are formed within the tissue owing to the disintegration of its neural elements." It is difficult to distinguish clinically, however, between the cysts which have developed as a primary degenerative process and those which are the end-result of vascular, edematous, traumatic and inflammatory lesions. Senile degeneration is one of the more common causes of the development of cystic spaces in the periphery of the retina and is a somewhat less frequent source of the formation of macular cysts and holes, according to Rones.[16] In the early stages, small spaces appear in the outer nuclear layer. Similar spaces then become visible in the inner nuclear layer, and for a time these two layers are separated by a thin septum. The disappearance of this septum causes the retina to appear as two thin sheets with delicate membranes stretching between them, forming large cystic spaces. On section, these spaces are usually found to be empty, though at times an albuminous coagulum is seen in them. The membranes stretching between the two limiting membranes of the retina are the stretched elongated Mueller's fibers, the true retinal layers having atrophied. Holes in the retina are formed by the breaking down of the limiting membranes. Duke-Elder[7] states that "cystic degeneration occurs with great regularity to a well-marked degree in the normal eyes of old people. It is the rule also in myopic degeneration (Hannssen, 1925)[9b] in which condition it is not uncommon even in comparatively early life (Ochi, 1927).[13b] Iwanoff (1865)[11a] found no instance in 20 globes of children under 8, in 12% of patients between 20 and 40, and in 50% of eyes between 50 and 80 years."

Cystoid degeneration of the peripheral part of the retina can rarely be recognized ophthalmoscopically and its only clinical importance is its possible rôle in the production of detachment of the retina. Cystoid degeneration of the macular retina, however, is of considerable clinical

importance since it eventuates always in loss of central vision. Duke-Elder[7] states: "At first, cystic spaces are formed in the retinal substance which may be visible, particularly with red-free light with which a typical honeycomb appearance is produced of small flecks in the central area (the vesicular macular edema of Nuel, 1908); eventually on rupturing these may produce a depression in the central area if they are confined to the inner layers of the retina, or a complete macular hole if the whole thickness of this tissue is involved (the retinitis atrophicans of Kuhnt, 1900). A hole in the macular retina is recognized ophthalmoscopically as a dark red circular punched out appearing spot about $\frac{1}{4}$ to $\frac{1}{3}$ disk diameter in size, usually directly in the fovea but occasionally slightly eccentrically placed. Its edges are usually clean cut but occasionally slightly ragged residuals of the anterior wall of the cyst are seen. At times the lesion is recognized in the stage of a thin walled cyst before rupture occurs. The dark red color of the lesion is due to increased visibility of the underlying choroid. Around a recently developed hole a halo of mildly edematous retina may be seen at times. Flat or shallow detachment of the retina surrounding the hole may develop in some instances. Probably the majority of macular holes are of traumatic origin, resulting from contrecoup rupture or from concussion or contusion edema of the retina. However, a fair number of cases are seen in elderly individuals, in whom they may develop as a sequence of simple senile cystoid degeneration of the retina or of the atrophy of the retina secondary to sclerosis and atrophy of the choriocapillaris, and occasionally as a complication of chronic edema of the retina resulting from circulatory insufficiency."

According to Rones,[15,16] the pigment epithelium of the retina is affected early by senile changes in the choroidal vessels and the resultant atrophy of the choriocapillaris. There is both degeneration and proliferation of the pigment cells and the pigment granules become small and round in form and are scattered over the basal membrane causing an irregularity and clumping of the pigment ophthalmoscopically. Associated with this there may be "an atrophy of the retinal periphery, with a decrease in the nerve fibres, ganglion cells, and inner nuclear layer, together with a disappearance of the rod and cone elements and a hypertrophy of connective tissue. The pigment epithelium becomes sparser, and pigment granules wander into the retina." This pathologic process undoubtedly explains the pigment migration into the periphery of the retina visible ophthalmoscopically in many elderly individuals, especially in those with cardiovascular disease, which is often sufficient in amount to simulate familial pigmentary degeneration of the retina or healed choroidoretinitis. In some instances, these changes may be associated with concentric contraction of the fields of vision. In most cases, however, there is no subjective disturbance of vision.

The subject of arteriolosclerosis and arteriosclerosis involving the vessels of the retina cannot be considered in detail here. Its proper consideration would require a separate and individual review. In very brief fashion, the view of Rones[15,16] may be quoted: "When the arterioles of the body (including those in the retina) are involved in the diffuse type of hyalinization of the media, there are found as ocular complications a diversity of hemorrhages and exudates, while general bodily resultants are hypertension and cardiac and renal impairment. . . . . Pathologically the changes (of arteriosclerosis) occur in the intima of the larger retinal vessels. The intima shows an increase in thickness due to a proliferation of connective

and elastic tissue, with a deposition of lipoids. This thickening is usually of a nodular character, so that small plaques project into the lumen of the vessel causing localized constrictions of its calibre. Clinically, this pure type of arteriosclerosis is observed in elderly individuals without any associated hypertension." This type of arteriosclerosis seems to be rare except in the central artery of the retina in the optic nerve or in its primary branches on the papilla where it may be the cause of some cases of obstruction of the central artery.

In the words of Rones,[15,16] "The eye is subject to changes in all of its tissues with advancing age. . . . . It is important to be able to recognize these senile variations clinically, so as to distinguish them from pathological lesions (*sic*). However, this is often a difficult matter, for numerous diseases of the eye are most common in those years when senile changes occur, and it is of interest to attempt to relate the aging phenomena to the etiology of the disease. . . . . It must be borne in mind that the relationship between tissue age and chronological age is not an exact one. Some individuals have advanced senile changes in their tissues at 40 years of age, while in others there is singularly little evidence of this at 80. . . . . Nevertheless it will be found that in every individual past the age of 40 years the ocular tissues will show alterations that fall into the senile classification, even though they are only in the beginning stages." In the causation of all these degenerations, the changes in the vascular system seem to be of primary and fundamental importance.

Many authorities are of the opinion expressed by Behr[3] that the macular degenerations, which are the most serious of the so-called senile lesions of the retina and choroid from the standpoint of visual disability, are essentially abiotrophic, that is to say a more or less inherited or familial wearing out of the tissue at a certain but variable age. However, Berens[4] calls attention to the important rôle played by changes in circulation and in the vascular system, some of which may be prevented, controlled, or at least moderated by the prophylactic or early removal of infections, focal or otherwise, and the avoidance of overindulgence in alcohol or tobacco, especially in advancing years. In Heath's[10] opinion a low fat and carbohydrate diet is of importance in the control of certain macular degenerations. Piersol[14] notes that evidence is being accumulated to show that diet plays an important part in human longevity and that a well-balanced, optimal diet, rich in vitamins during youth and early adult life, is important in preventing or delaying the onset of senile tissue changes. In addition to the advisability of proper dietary habits, Berens[4] emphasizes the importance of hygienic living, adequate rest and sleep, sunshine and moderate exercise adjusted to the individual's capabilities. In conclusion, the words of Piersol[14] are well worth quotation: "Heretofore, the physician has somewhat lacked interest in disease as it appears in the older person, looking on it as irremediable and inevitable. If the medical problems of old age are to be successfully met, he must abandon his defeatist attitude and approach the management of such problems in a spirit of greater constructiveness and optimism. It will then be possible for him to do much to prolong life, relieve suffering and mitigate in no small degree the handicaps and infirmities of old age. . . . . If the physician is to meet his obligations to the aged, he must constantly bear in mind the importance of controlling those presenile states which if allowed to go unheeded will lead to chronic visceral disease, for which little can be done."

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PHYSIOLOGY

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Roentgen ray Diffraction Patterns of Striated Muscles (Effects of Stimulation, Rigor, Drugs). M. SPIEGEL-ADOLF, E. W. ASHKENAZ, KATHRYN MCHALE, Fellow, A. A. U. W., and G. C. HENNY (Departments of Colloid Chemistry and Physics, Temple Medical School). Former Roentgen ray diffraction studies of globular proteins were extended to studies of parallel fibers of sartorius muscles of *Rana pipiens*. Our apparatus permits the study of living material under various conditions, the exposure time being cut down to 6 minutes. While powdered dried muscle shows only 2 diffuse rings, identical in their spacings to the usual protein pattern, wet and dried muscle fibers indicate orientation in both rings, perpendicular to the long axis of the fibers. A comparison between the patterns of wet and dried muscles based on statistical computations indicates that only a small amount of water is located intramolecularly. The reversibility of the changes produced by drying is practically complete. Stretching of the muscles by weights below the breaking point produces an additional well-defined diffraction line, identical with one observed in stretched frog tendon and also with a similar line in powdered muscle nuclei.

Electrical stimulation, caffeine poisoning and mechanical stimulation cause disappearance of orientation in the Roentgen ray diffraction pattern if the muscle is allowed to shorten. Conversely, after electrical stimulation, stretching of such a contracted muscle restores the orientation. Rigor-inducing procedures (death, heat, chloroform) show definite changes of the Roentgen ray diffraction patterns: disappearance of orientation in all instances, characteristic sharpening of back-bone reflection, new spacing

upon heating and increased membrane permeability, as in chloroform poisoning. Lactic acid produces similar losses in orientation in concentrations over 0.005 N; hypertonic salt solutions produce a loss in orientation in immersed, cut muscles, parallel to the known loss in birefringence. Such muscles, after washing and drying, show salt rings superimposed upon their own diffraction patterns, thus indicating an increased permeability of the cell membranes. Similar changes can be observed in muscle in which the NaCl of Ringer's solution has been replaced by KCl, showing thus its biologic effectiveness.

Insect Nerve Sheaths and Insecticide Penetration. A. GLENN RICHARDS, JR. (Zoölogical Laboratory, University of Pennsylvania). Insect nerves are non-medullated but are surrounded by a bound lipid sheath of submicroscopic thickness. The lipids are quickly released and extracted by alcohol but the fiber tract areas can be stained with Sudan after formalin fixation. Polarized light studies on living nerves show the presence of metatropic sheaths, the entire nerves having the closest balance of positive and negative components of any known nerves. Insect nerve cords exhibit a high degree of photoelasticity, and the increase in amplitude of birefringence is a fairly constant reading. Chemicals which cause a decay of the axoplasmic birefringence also decrease or destroy the elasticity.

The distribution of the lipid sheaths is positively correlated with the penetration of oils and oil-solvents from tracheæ as shown by selective staining from lipid dyes used to mark the material applied. It seems likely therefore that these lipid sheaths condition the penetration of such materials into the nervous system, at least when the materials are diffusing from tracheæ.

Extensive studies now being performed show that the various neurotoxic insecticides may have different effects on the optical and elastic properties. Lipid solvents eliminate the lipid sheaths; some insecticides cause a particulate degeneration of the lipids, others attack the axoplasm, and others may affect both axoplasm and sheath in different degrees. For insect nerves where the proteins and lipids are so closely balanced optical analyses are far more sensitive than ordinary histopathologic methods.

Studies on Bioassay of Penicillin. LIDA F. HOLMES and JOHN S. LOCKWOOD (Harrison Department of Surgical Research, University of Pennsylvania). Foster and Woodruff (*J. Bact.*, **46**, 187, 1943) have described a method for assay of penicillin, testing turbidity of a staphylococcus culture. A method based on the same principle has been devised in this laboratory which requires only a 2 hour period of incubation and which will detect concentrations as low as 0.01 unit per cc. The test can be adapted to examination of colored fluids containing penicillin by centrifuging down the staphylococci and resuspending them in distilled water for reading their turbidity.

The object of our investigation was to find a sensitive, rapid test for determination of penicillin levels in serum. However, when we conducted turbidimetric tests with serum containing known added amounts of penicillin, several difficulties were encountered: (1) Natural antibody to the staphylococcus causes inhibition of growth in certain dilutions of serum.

(2) It was found that serum interfered with the action of penicillin. Likewise, horse and rabbit serum and human ascitic fluid contain an anti-penicillin factor. Dialysates of these fluids are also antagonistic to penicillin, and the inhibiting substance may be concentrated by lyophilization of the dialysates. This unknown anti-penicillin substance resists heating at 60° C. for 30 minutes, but is destroyed by boiling for 10 minutes. Investigation of its properties is being continued.

The Use of Horse Brain Thromboplastin for the Quantitative Determination of Prothrombin. LOUIS A. KAZAL and L. EARLE ARNOW (Department of Biochemistry, Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.). Preparations of horse brain thromboplastin, prepared essentially according to Quick's directions for rabbit brain, clotted citrated human plasma in 16.8 to 25.8 seconds, when optimal concentrations of calcium chloride solution and thromboplastin were used in the Quick test. The optimal concentration of calcium chloride solution was 0.184% for the plasma used by us. Dilutions of the brain suspension with an equal volume of water yielded preparations that gave minimal clotting times.

Although rabbit brain thromboplastin is more active than horse brain thromboplastin, it appears that the horse brain preparation is suitable for the quantitative determination of prothrombin. With plasmas of known prothrombin contents, determinations usually could be made to within 9% of the theoretical concentration of prothrombin. The differences in prothrombin concentrations found with the two thromboplastins were not greater than 6%. Except in 1 case, with plasmas of unknown prothrombin concentration the difference in the concentrations determined with horse and rabbit thromboplastins was not greater than 13%.

Horse brain thromboplastin has been lyophilized and then stored under vacuum at 5° C. for 14 months with little or no loss of potency.

BOOK REVIEWS AND NOTICES

THE COMMON FORM OF NIACIN AMIDE DEFICIENCY DISEASE: ANIACINAMIDOSIS. By WILLIAM KAUFMAN, PH.D., M.D. Pp. 62. Bridgeport, Conn.: Yale University Press, 1943. Price, $3.00.

UNDER the name of a specific vitamin deficiency called aniacinamidosis—probably because niacinamide is the substance used for its therapy—is described a complex of almost innumerable symptoms ranging from neurasthenic manifestations to calluses and corns. Nothing that could be called valid scientific evidence is to be found in the entire 58 pages, but it is written in a soothing, pseudoscientific manner that might easily deceive the uninformed.

E. W.

FINGER PRINTS, PALMS AND SOLES. An Introduction to Dermatoglyphics. By HAROLD CUMMINS, PH.D., Professor of Microscopic Anatomy, Tulane University, School of Medicine; and CHARLES MIDLO, M.D., Associate Professor of Microscopic Anatomy, Tulane University (Formerly Assistant Professor of Anatomy, Louisiana State University). Pp. 309; 149 illus. Philadelphia: The Blakiston Company, 1943. Price, $4.00.

THE chief purpose of the authors in writing this book was "to fill the want of a comprehensive treatise on dermatoglyphics." They have presented the subject under the following divisions: Part 1, Orientation; Part 2, Methodology and Description; and Part 3, Biology. Part 1 might have been improved and its seriousness more appreciated if the brief remarks on current popular interest in finger printing and the dactylomancy incident had been omitted. Part 2 contains the methods and procedures necessary for anyone actively working in the field. Much of this part is covered adequately in books already existing but its inclusion in this book is useful in interpreting portions of Part 3. It is in the last part where the scientific importance of the work lies. Here in about one-half the book and in an interesting and effective manner the authors have marshaled the available data on the fundamental biologic phases of dermatoglyphics. This publication should find wide usefulness among students of biology and workers in identification. R. W.

A TEXTBOOK OF MEDICINE. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College, etc., Associate Editor for Diseases of the Nervous System; and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College, etc. Sixth ed., revised and entirely reset. Pp. 1566; 195 illus. Philadelphia and London: W. B. Saunders Company, 1943. Price, $9.50.

THIS already excellent text has been still further improved by changes in the format (such as the 2-column, slightly larger page), and in the text. The Preface lists 11 new articles on subjects not covered in previous editions, 31 new treatises on subjects previously covered, and 2 new features—introductory chapters to groups of diseases (*e. g.*, Rickettsiæ, Pneumococcic Infections, Metabolism, the Blood, etc.); and a list of normal values for the commoner, but constantly growing laboratory tests. All this is a direct reflection of the efficient industry of the Editor, without which a single volume composed by so many authors would be almost surely a failure, even with the eminent list of authors that this work has gathered together. E. K.

PHYSIOLOGY OF THE NERVOUS SYSTEM. By JOHN F. FULTON, M.A., D.PHIL., D.Sc. (OXON.), S.B., M.D., Sterling Professor of Physiology, Yale University; formerly Fellow of Magdalen College, Oxford. Second ed. Pp. 614; 112 figs. New York: Oxford University Press, 1943. Price, $9.00.

THIS edition of Fulton's book should enjoy great popularity with the medical student (because of the clarity with which complicated mechanisms are presented), with the physician (because of the stress laid upon the practical applications of the material presented), and with the physiologist (because of the completeness of the text and its 66 page bibliography). It has been brought up to date by Dr. Fulton and his collaborators, particularly in the chapters dealing with the neurohumoral theory of nerve excitation and with respiration. A more detailed discussion of the effects of oxygen lack and cerebral anemia upon the nervous system as a whole would have been useful in wartime, with its attendant high altitude flying, dive bombing, and exsanguinating wounds. J. C.

MEDICAL CLINICS ON BONE DISEASES. A Text and Atlas. By I. SNAPPER, M.D., formerly Professor of Medicine, Peiping Union Medical College, Peiping, China. Pp. 225; 30 plates. New York: Interscience Publishers, Inc., 1943. Price, $10.75.

DR. SNAPPER'S book is a very interesting résumé of bone diseases, taking up in great detail von Recklinghausen's disease, Hodgkin's disease of bone, multiple myeloma, lipoid granulomatosis, osteomalacia, and other diseases involving the skeletal system. The author has had an exceptional opportunity in his wide clinical experience as former Professor of Medicine at the Peiping Union Medical College in China. Due to his familiarity with the frequency of these bone diseases, both in America and China, he is able to discuss very interestingly the pathogenesis and the relation of many of these diseases regarding their disturbed metabolism, their biochemical problems and the diseases of deficiency. The Reviewer enjoyed reading the text of this unusual compilation of rather rare bone diseases. The very beautiful plates with which his book is illustrated are especially deserving of mention. The clearness of detail reproduced both from the Roentgen rays and photomicrographs of the cases under discussion are an indication of the huge amount of clinical material that must have been at his disposal. P. C.

THE CONQUEST OF EPIDEMIC DISEASE. A Chapter in the History of Ideas. By CHARLES EDWARD AMORY WINSLOW. Pp. 411. Princeton, N. J.: Princeton University Press, 1943. Price, $4.50.

THIS story of man's epic struggle against epidemic disease is more than a fascinating saga—it is a study in human evolution. So dramatic and recent has been the conquest of the grim horseman of pestilence that the gradual growth of concepts through plague-ridden centuries of dreadful experience is prone to be forgotten. Public health victories during the last hundred years are familiar themes, but Professor Winslow has reviewed the records of 3000 years and under his skilful pen the slow emergence of social consciousness of the controllable nature of contagious disease takes form—not by propounding but compounding the slow-won facts to the strategy of community effort rather than individual medical care which has brought plagues under control.

The reconstruction of mental attitudes toward the external cause of contagious disease—from primitive notions of malignant demons, the wrath of God, astrologic influences, naturalistic concepts of Hippocrates, epidemic constitution of schoolmen and primitive biologic experiments, to the germ theory of disease, which gave instruments for sanitary adjustment of our environment through processes of civilization—is a study in mental evolution. Unconsciously, perhaps, one recognizes the headlands of progress, not so much in

the scholarly deductions of authorities as in the simple experiments of novices. Even the astute comprehension of Fracastorius as to the essential nature of contagion could not be assimilated by the intellectual and spiritual leaders of the time, and 300 years of evolution were required for the great sanitary awakening in the first half of the 19th century, and for the conception of *contagium animatun* of Kircher, Redi and Leeuwenhoek to generate a biologic theory of disease. The discoveries unleashed by the germ theory constitute a glorious chapter in science, and the technical application of these discoveries during the present century is one of the great achievements in human welfare.

The book is thus of general interest and a *must* for every student of public health and welfare and a *should* for every intelligent person. It is a tale told to quicken the dullest imagination and should adorn the shelves of the most modest library. W. W.

MICROSCOPIC TECHNIQUE IN BIOLOGY AND MEDICINE. By E. V. COWDRY, Professor of Anatomy, Washington University, and Director of Research, The Barnard Free Skin and Cancer Hospital. Pp. 206. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.00.

THE author presents a new type of book for investigators in the field of biology and medicine who are interested in techniques for the preparation and micro-examination of tissues, animal parasites, protozoa, bacteria, rickettsiæ and viral elementary bodies.

The text is arranged in alphabetical order with headings containing cross-references to other titles appearing in the text. Each heading is discussed, not in voluminous detail, but in concise manner giving exact and specific information. It is not intended to be an encyclopedia but a ready reference text on recognized physical, chemical and biologic means for studying the minute structure of living matter.

Great emphasis is placed on fixatives, dyes and stains, microdetection of enzymes, methods of pH determination, histospectroscopy, microincineration techniques, microchemical reactions and *in vivo* examination of tissue. Especially important are the references to the literature where more complete articles and reviews of the individual subjects may be found as well, as references to good texts on each subject. F. E.

DOCTOR IN THE MAKING. The Art of Being a Medical Student. By ARTHUR W. HAM, M.B., Associate Professor of Anatomy, in Charge of Histology, Faculty of Medicine, University of Toronto; Honorary Secretary of the Banting Research Foundation; and M. D. SALTER, M.A., PH.D., Lecturer and Research Fellow in the Department of Psychology, Faculty of Medicine, University of Toronto. Illustrations by JEAN MCCONNELL. Pp. 179. Philadelphia, London and Montreal: J. B. Lippincott Company, 1943. Price, $2.00.

Two Canadian medical teachers, an anatomist and a psychologist, have combined to put before medical students and those considering a medical career the motives and medical equipment that promote progress and the common enemies that hinder success. We wish that this review would fall into the hands of these two groups; the time required to read and really possess its contents could not be better spent otherwise. Study habits, attitudes toward medical topics and toward those doing the instructing, general personality characteristics and ways of improving them, understanding and applying the scientific method, the proper allocation of time—such are the topics simply and clearly set down for consideration.

Especially appealing to the Reviewer is the chapter on the importance of pre-medical and pre-clinical subjects—"There is no mysterious course in later years of medical school that teaches you to become a doctor." Training for practice begins before entering school, and continues throughout life; but it is

especially in the earlier courses—and only there for the vast majority—that the basic knowledge and attitudes can be obtained on which the new edifices of knowledge can be erected that are required to keep a physician "up to date."

How not to study or waste the time spent in evening work, how to assimilate lectures, how to organize one's knowledge, how to understand (as opposed to memorizing), and to appreciate the meaning of words, these are all matters which, to the Reviewer after a considerable experience in teaching medical students, are of prime importance in the student's self-education, not to mention the passing of examinations. How to use textbooks and journals and the medical library, the importance of terms and definitions (*i. e.*, semantics) are phases that are particularly lacking in the equipment of most students.

The chapter, Your Child-Self, really a bird's-eye view of the practical psychology of the individual, could be studied with profit by medicos of every age and condition.

In short, this is an excellent aid on "the right road to learning." Incidentally, we hope that its wartime paper will stand the strain of heavy usage. One could wish that Lippincott's had an endowment fund that would place a copy in the hands of every pre-medical student, if it were not that things so acquired are apt to be correspondingly evaluated. Last but not least, the student should be attracted by its brevity. E. K.

URINE and URINALYSIS. By LOUIS GERSHENFELD, P.D., PH.M., D.Sc., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Second ed. Pp. 304; 42 figs. Philadelphia: Lea & Febiger, 1943. Price, $3.25.

IN this new edition there is a chapter on the history of methods of analysis of urine which forms an excellent background to the work that the author wishes to present. The physiology of the urinary tract is discussed to promote better correlation of the laboratory tests to be described. The most modern methods of qualitative and quantitative analysis of urine are presented in detail. Normal and abnormal findings of these examinations are discussed.

In addition to the chemical examinations themselves, there are chapters on the bacteriologic and microscopic analysis of urine, as well as renal function tests. The chapter on analysis of urinary calculi presents a method which has been generally acceptable, but is actually obsolete in the light of recent publications on the subject.

An appendix gives a description of the apparatus and reagents used in urinalysis.

Here arranged in a single volume is information concerning the urine which could otherwise be obtained only by covering many texts and papers on the subject. There is nothing new or astounding about the information presented; however, it seems justifiable to have such a volume for the use of the busy pharmacist, chemist, bacteriologist, technician or physician. L. La T.

REACTION TO INJURY. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents. By WILEY D. FORBUS, M.D., Professor of Pathology, Duke University and Pathologist to the Duke Hospital. Pp. 797; 523 illus. (20 in color). Baltimore: The Williams & Wilkins Company, 1943. Price, $9.00.

THIS fine book is an important contribution to pathologic literature. The difficult subject of inflammatory diseases is beautifully organized. A new, but most logical, approach to this problem is used. Pathogenesis is emphasized, etiology being delegated to a secondary place. This should be of distinct advantage to the student, to whom the variety of inflammatory responses often seems infinite.

The book is planned around this basic definition: the essential element in disease is the reaction of the cells of the body. This reaction may be of 3 types: (1) by active resistance; (2) by passive submission; (3) by effecting an adaptation. In Part I these are discussed and all types of injurious agents are considered—trauma, chemical and physical agents, bacteria, fungi, protozoa, worms and so forth. Part II, the body of the book, a discussion of the active resistance type of reaction, includes detailed descriptions of bacterial infections, rheumatic fever, nephritis, virus diseases, and granulomata, to take a few examples. Unfortunately, Parts III and IV, a discussion of the submissive and adaptive reactions, are not completed as yet. A second volume is projected for these.

The book is magnificently printed and illustrated. Nearly 90% of its 532 figures are original, many in excellent color.

Many pathologists may object to the strong teleologic flavor of some of the terms used. These are often difficult to eliminate without sacrificing emphasis and clarity.

As a special text on inflammatory diseases, this book should prove extremely valuable to the student of pathology. As the work limits itself to this special field, the 2d-year student must naturally use it in conjunction with a standard text. With this book, however, Dr. Forbus has made a fresh and valuable contribution to the pathologic literature of inflammatory disease. W. S.

ADDENDUM TO THE CHEMISTRY OF THE AMINO ACIDS AND PROTEINS. Edited by CARL L. A. SCHMIDT, M.S., PH.D., Professor of Biochemistry and Dean of the College of Pharmacy, University of California. This is a supplement to the Second edition. Pp. 155; figures and tables. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, $5.00.

As the title implies, this book is not a revision of the original volume of *The Chemistry of the Amino Acids and Proteins*. Instead it is more in the nature of an addition, even to the extent of continuing the reference and page numbering from the original. The chapter divisions and order are unchanged except in a few cases in which there was no revision. For the most part the authors are also the same. The chapter on nutrition has been revised by Dr. H. J. Almquist, instead of Dr. R. W. Jackson, and Dr. C. L. A. Schmidt has taken over the work of several of the former authors especially those from foreign countries. As in the original volume, the various chapters are written in a highly technical manner and in many cases data from original articles have been included. The book is of particular value to those working in and familiar with the field of protein chemistry, but those whose major interests lie in other branches of biochemistry will also find this book of value. J. J.

PRINCIPLES AND PRACTICE OF REHABILITATION. By JOHN EISELE DAVIS, M.A., Sc.D., Veterans Administration Facility, Perry Point, Md. Pp. 211; various tables and charts. New York: A. S. Barnes & Co., Inc., 1943. Price, $3.00.

THIS experienced rehabilitator tells us that the modern approach to our problem is medical, psychologic, psychiatric and vocational. Among other chapters are those on Effect of War and Depression; Psychiatric Approach, General Consideration; Elemental Principles of Mental, Nervous and Physical Reconstruction; Therapeutic Objectives and Results; Handicraft and Art. The recreational discussions are among the best given, particularly those of Interest and Effort Theories, wherein are reports on dementia præcox, manic depressive and dementia paralytica patients. A useful feature is an Appendix giving 6 case histories from the New Jersey Rehabilitation Clinic. No mention is made of the Rorschach test, which has both diagnostic and prognostic value.

N. Y.

PYE'S SURGICAL HANDICRAFT. Edited by HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Surgeon, Italian Hospital; Consulting Surgeon, Clacton Hospital and the County Hospital, Chatham; External Examiner in Surgery, University of Bristol. Thirteenth ed. Pp. 536; 534 illus. Baltimore: The Williams & Wilkins Company, 1942. Price, $6.00.

THIS is really a manual of minor surgical techniques. The scope extends from laboratory technique, bandaging, and first-aid through anesthesia and general surgery to minor surgical procedures of otolaryngology, ophthalmology, and dentistry and to the treatment of gonorrhea and syphilis. The purpose of the book is commendable in that it presents many of the techniques that are not included in ordinary textbooks and are learned by the intern only through observing the methods of older members of the profession.

The scope of material is apparently so extensive that it prohibits an adequate discussion of many of the individual subjects. The sections on fractures, although very brief, are excellent. H. Z.

A MEDICAL BIBLIOGRAPHY. A Check-list of Texts Illustrating the History of the Medical Sciences. Originally compiled by the late FIELDING H. GARRISON, M.D., and now revised, with additions and annotations by LESLIE T. MORTON, Librarian, St. Thomas's Hospital Medical School. Pp. 412. London: Grafton & Co., 1943. Price, £2.10s net. (About $10.00).

THIS useful book has an interesting provenance. The underlying idea goes back, like so many others, to William Osler, who suggested the compilation of such a list to Garrison. This appeared in the Surgeon-General's Index Catalogue in 1912 (vol. 17, Sec. S, pp. 89–178) and served its compiler "as a convenient scaffolding" for his great *History of Medicine*, which first appeared in 1913. A revised and enlarged list appeared in the Bulletin of the Institute of the History of Medicine in 1933, to which 1680 new entries have now been added by the English compiler. Thus Canadian, American and English scholars have collaborated to our advantage. This edition also contains many useful annotations, and—especially valuable in a work of this sort—good author and subject indices. It should be noted that the references are to entry numbers and that only the references to original works are given in Roman type.

The value of such a volume on one's shelves is considerably enhanced to the user if he early takes care to develop a sufficient acquaintance with its plan of construction to be able easily to identify the item sought. Thus, the simple fact that in each section the works are arranged in the chronologic order of their appearance at once changes an apparent heterogeneous assemblage into a simple and useful orderly list. The list of over 50 "Principal Headings" (p. vii) ranges from voluminous subjects such as Anatomy and Physiology (1072 references) to Epidemiology and Medical Ethics that are represented by 10 and 8 references, respectively. It includes rather haphazardly: Opera Omnia (80 references) and History of Medicine (182 references), various specialties, individual diseases, diseases of systems, Medical Biography (28 references), Bibliography (31 references), Lexicography (21 references), and so on. By way of further illustration, the first reference is to R. F. Harper's book (1904) *Hammurabi's Code*, the second to Joachim's (1890) *Ebers Papyrus*. The *Edwin Smith Papyrus*—the oldest of medical texts—is appropriately found under Surgery (Ref. 4734), as might be inferred from the "See also" reference to Surgery beneath the Principal Heading—"Collective Works."

To cover such a wide scope in 412 small pages obviously required strict discrimination. As Morton observes: "Much has been omitted that might have been included; it is hoped that nothing has been included which ought to have been omitted." Students of and writers on Medical History can hardly afford to be without this volume, which in view of the nature of the text will not be regarded as high priced. E. K.

THE DYSENTERIC DISORDERS. The Diagnosis and Treatment of Dysentery, Sprue, Colitis and Other Diarrhœas in General Practice. By SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P., Senior Physician to the Hospital for Tropical Diseases, Royal Albert Dock and Tilbury Hospitals; Consulting Physician in Tropical Diseases to the Dreadnought Seamen's Hospital, London; Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Medicine to the Admiralty and to the Royal Air Force; Lumleian Lecturer, Royal College of Physicians, 1941. Appendix by W. JOHN MUGGLETON, M.S.M., F.I.M.L.T., Technical Assistant. Second Ed. Pp. 629; 108 illus. (some in color). Baltimore: Williams & Wilkins Company, 1943. Price, $10.00.

SINCE December 7, 1941, there has been a general awareness in the medical profession that the so-called tropical diseases are of a great deal more significance than was formerly believed. In spite of the warnings of the medical corps of the Army and Navy, and in spite of outbreaks of dysentery, such as the one in Chicago in 1933, up to that time only an academic interest was taken in the subject by most of the medical men in the country, with the exception of those in the far South.

The second edition of this book will be received by a very much larger number of readers in the United States than was the first edition in 1939. The second edition is substantially the same as the first, but additions have been made by the inclusion of newer methods of treatment, such as the use of sulfaguanidine in bacillary dysentery.

The simplicity and lucidity of the writing make the mass of information this book contains easily available to everyone. The illustrations are excellent.

We recommend this book to all those interested in the subject, as well as to all those who should be interested in it. E. R.

PAIN. XXIII of the Association for Research in Nervous and Mental Disease. Editorial Board: HAROLD G. WOLFF, Chairman; HERBERT S. GASSER, M.D., and JOSEPH C. HINSEY, PH.D. Pp. 468; 166 illus.; 19 tables. Baltimore: Williams & Wilkins Company, 1943. Price, $7.50.

THIS volume is the product of 37 collaborators, who discuss 32 different topics. Some of these are: the pain threshold in man; central representation of pain; insensitivity to pain in man; the genesis of pain from the joints; pain from the bladder, ureter and kidney pelvis; pain from the pleura and pericardium; pain from the bronchi and lungs; pain from the digestive tract; pain of peptic ulcer; cardiac pain; effect of extracardiac pain on the heart; management of intractable pain by posterior rhizotomy; management of intractable pain by chordotomy; experimental studies in pain from the nasal and paranasal structures; surgical methods for relief of pain in the head and neck; headache mechanisms.

On page 242, where "scalp and neck muscles and pain" are discussed, the condition which is given several names but which would most appropriately be designated myalgic headache, is given scant and unsatisfactory consideration. As a general disorder it has been termed "an everyday affection," of which some of the local expressions are headache, stiff neck and lumbago. Its manifestations are particularly apt to appear in tendinous structures, refrigeration is often a factor in their production, and the literature on the subject is abundant. For the general condition, Gowers coined the term, "fibrositis." The disorder is best known to the Scandinavians, and anyone properly trained in the Swedish system of massage, can demonstrate the presence of these indurated muscle areas, by pressure over them with lubricated fingers and by passive stretching of the involved muscles, when sharp pain will be experienced. The Swedes not only find these "sore spots," but they have a skillful method of removing them, to the surprise and comfort of their patients.

In the discussion that followed each presentation of this Symposium of the Association, there was active participation. The Chairman of the Board must have experienced a sense of gratification, since it had been his hope that there would be a sustained effort for a better understanding of perception, leading to better management of pain as a simple sensory experience; and with additional knowledge of the autonomic, emotional and attitudinal reactions in persons of different cultural and individual experiences, the sounder should be our care of the ill.

N. Y.

INTRODUCTION TO PHYSIOLOGICAL AND PATHOLOGICAL CHEMISTRY. By L. EARLE ARNOW, PH.G., B.S., PH.D., M.B., M.D., Director of Biochemical Research, Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.; Professor of Chemistry, Bryn Mawr College Summer School of Nursing, 1941–43. Introduction by KATHARINE J. DENSFORD, B.A., M.A., R.N., Director of the School of Nursing and Professor of Nursing, University of Minnesota. Second Ed. Pp. 574; 142 figs.; 31 tables. St. Louis: C. V. Mosby Company, 1943. Price, $3.75.

THIS volume was written originally for use by students in nursing. Its content follows closely the outline suggested by the National League of Nursing Education (1937). Part I is a general introduction to inorganic and organic chemistry, given in sufficient detail to aid in understanding material presented later. Part II gives a discussion of physiologic and pathologic chemistry, including chapters on hormones, vitamins and nutrition. Part III is devoted to selected laboratory exercises covering most of the usual procedures along with tests for certain hormones and vitamins. Approximately 30 pages in the Appendix describe home methods for stain removal from fabrics.

Numerous descriptive diagrams and pictures of the physical changes produced by various diseases are presented along with the text. Minor changes have been made in this second edition. Newer members of the vitamin B complex, intestinal bacterial synthesis of vitamins, the sulfonamides, and transmethylation are among the newer topics discussed. Also certain clinical tests are discussed more extensively.

This text should be satisfactory for the students for which it was prepared.

H. V.

TREATMENT OF EXPERIMENTAL DATA. By A. G. WORTHING, Professor of Physics, University of Pittsburgh; and JOSEPH GEFFNER, Weirton Steel Company. Pp. 342. New York (16): John Wiley & Sons, Inc., 1943. Price, $4.50.

THE problems of the proper presentation of experimental data and the evaluation of data presented by others have probably, in one form or another, confronted most individuals engaged in experimental work. Many have perhaps sought vainly in the past for a single text which deals adequately with various aspects of this subject. The need for a unified presentation has been met by Worthing and Geffner's new book.

Treatment of Experimental Data is a concise, well-organized text. It deals systematically with such subjects as criteria for judgment of goodness of data, fit of mathematical equations, construction of tables and graphs, preferential use of equations, tables or graphs, etc. In addition to these general topics, the text affords an adequate treatment of the essentials of correlation. There is an excellent appendix upon the subject of determinants, whose value in the solution of simultaneous equations (which often crop up in biomathematics), does not appear to have been sufficiently recognized by biologists.

This text should prove of value to most graduate students, and to all workers in the field of medicine and biology who may wish to become better acquainted with the mathematical bases of treatment of experimental data. The Reviewer is glad to recommend this unique text most highly.

D. D.

PSYCHOLOGICAL MEDICINE. By DESMOND CURREN, M.B., F.R.C.P., D.P.M., Psychiatrist and Lecturer in Psychological Medicine, St. George's Hospital, and Honorary Psychiatrist to the Maida Vale Hospital for Nervous Diseases, London; Temp. Surgeon Captain R.N.V.R., and Consultant in Psychological Medicine in the Royal Navy; and ERIC GUTTMANN, M.D., L.R.C.P. (ED.), Neuropsychiatric Specialist, Emergency Medical Service; Formerly Research Psychiatrist, the Maudsley Hospital, London, and Research Neuropsychiatrist, Nuffield Dept. of Surgery, Oxford. Foreword by J. J. CONYBEARE, D.M. (OXON.), F.R.C.P., Physician to Guy's Hospital, London. Pp. 188; 21 illustrations. Baltimore: Williams & Wilkins Company, 1943. Price, $3.50.

IN this book, designed for students, general practitioners and Service physicians, the text is divided into two parts: A Short Introduction to Psychiatry, and War-time Psychiatry. In the former, most of the topics are well discussed; they are Introductory, Ætiology of Mental Disorder, Symptoms in Mental Disease, Psychiatric Case-taking, Treatment, Constitutional Anomalies, Organic Syndromes, Drug Addictions, Schizophrenia, Affective Reaction Types, Hysterical Reactions, and Legal Aspects of Mental Illness (since the book is published in America, inclusion of the English and Scotch laws pertaining to mental diseases, and exclusion of our own, renders that portion of the book of but little value here).

As regards psychoanalysis: "it has tended to become a special calling for the pursuit of which neither a psychiatric nor a general medical training has always been considered essential. . . . . Such results as are available, do not seem to be any better than those obtained by less expensive and laborious methods." Under Intelligence Tests, no mention is made of the Rorschach procedure, which several countries have used successfully in their examinations of service men.

The part on War-time Psychiatry has but one defect—it is much too brief. There are excellent short discussions on Principles of War-time Psychiatry, Examination of Service Men, Clinical Syndromes, Management and Treatment, and Psychiatric Aspects of Head Injuries. N. Y.

BIOCHEMISTRY FOR MEDICAL STUDENTS. By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Third Ed. Pp. 476; 39 illus. Baltimore: Williams & Wilkins Company, 1943. Price, $4.50.

EXIGENCIES of the war have prevented the author from making very many changes in the material presented in the third edition. A short chapter on the Chemistry of Respiration has been added. Rearrangement of the text has allowed the addition of some other new material.

The presentation of the general descriptive matter is both adequate in scope and detail. It is to be regretted that the weakest part of the volume is concerned with the metabolism of foodstuffs within the tissues. Most of the fundamental work of the last few years has, of necessity, been omitted. It is hoped that this (serious) omission will be corrected in any future edition.

H. V.

ELEMENTS OF MEDICAL MYCOLOGY. By JACOB H. SWARTZ, M.D., Assistant Professor of Dermatology, Harvard Medical School and Postgraduate School, Boston, Mass., with an Introduction by FRED D. WEIDMAN, M.D., Professor of Dermatological Research, University of Pennsylvania, Philadelphia, Pa. Pp. 179; 79 figs; 1 table. New York: Grune & Stratton, Inc., 1943. Price, $4.50.

THIS book is not a definitive text but is designed to serve the medical student or practitioner as a guide in the study of fungous diseases. Discus-

sion of certain rarer diseases has been sacrificed for simplicity and conciseness of content and expression. The book contains a general discussion of fungi and a glossary of terms which should prove helpful to the reader for orientation. One chapter is devoted to the laboratory diagnosis of fungous infections. Other chapter headings are: Blastomycetes (yeast-like fungi); Microsporum; Trichophyton; other pathogenic fungi, including Gilchrist's organisms, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, chromoblastomycetic fungi, Sporotrichum, Actinomyces, and Histoplasma. A short chapter is devoted to common contaminants and probable pathogens which may be encountered from the air. There is a very brief discussion of immune reactions (trichophytin and oidiomycin tests) and the effect on fungi of sulfanilamide and its derivatives. A chart, measuring 15 x 31 inches, gives much important information on the clinical pictures and mycologic findings for many of the important fungi. The illustrations are very good. H. M.

BIOCHEMISTRY OF THE FATTY ACIDS and Their Compounds, the Lipids. By W. R. BLOOR, Professor of Biochemistry and Pharmacology, The University of Rochester, Rochester, N. Y. American Chemical Society Monograph Series. Pp. 386; tables and charts. New York: Reinhold Publishing Corp., 1943. Price, $6.00.

WITHIN the last few years there has developed a marked interest in the chemistry and function of the lipids. This is due in part to the development of more adequate analytical tools, and also to a greater appreciation of the ubiquitous rôle of these compounds in the life processes of all living tissues.

In this book the field of discussion is limited to those naturally occurring substances chemically and metabolically related to the fatty acids. In the preliminary chapter the descriptive and analytical chemistry of the compounds to be discussed is outlined. Subsequent chapters deal with digestion and absorption, lipids of the blood, lipids in tissue, lipid metabolism, and the lipids of secretions and excretions.

We are fortunate in having such an eminent leader in this phase of biochemistry summarize and correlate the evidence accumulated up to the present. While many phases of the subject do not permit a complete picture to be developed, this review by Dr. Bloor focuses attention upon future problems. Everyone having an interest in this phase of biochemistry will find this book of great value. H. V.

UROLOGICAL DISEASES OF PREGNANCY. By E. GRANVILLE CRABTREE, M.D., Urologist to the Boston Lying-In Hospital. With a signed chapter by GEORGE C. PRATHER, M.D., Assistant Urologist to the Boston Lying-In Hospital. Pp. 472; 158 figs., several in color. Baltimore: The Williams & Wilkins Company, 1942. Price, $5.00.

IN the not distant past, when one thought of the urologic aspects of pregnancy, the subject of pyelonephritis of pregnancy came to mind. Other considerations were not frequently thought of. Dr. Crabtree's book is the first comprehensive treatise on the urologic aspects of the pregnant state. It represents a work of over 25 years. The information upon which the text is built could only have been obtained by extensive study of the literature and by extensive personal experience.

The great advance in the state of knowledge, concerning these subjects, which began in 1930, is recorded. The application of basic principles of urologic study to pregnant women in health and disease had to await the development of the urologic approach. This knowledge springs from the use of the modern cystoscope, retrograde pyelography, intravenous urography, renal function tests, and blood and urine chemistry.

The book contains 36 chapters and is divided into 2 parts. Among the subjects covered in the first part of the book are anatomy and physiology of

pregnancy, effect of pregnancy on preëxisting pathologic conditions in the urinary tract, and urinary tract infections. The predisposing causes of urinary infections and their treatment in the light of most recent advances are thoroughly covered. There is a separate chapter on the bladder and the effect of pregnancy, delivery, and puerperium upon it.

The technique of cystoscopy and other urologic examinations as particularly applied to the pregnant state is discussed in the second half of the book. The following subjects are discussed in detail in this section: toxemia of pregnancy, hematuria, lone kidney, tuberculosis, calculus, tumor, polycystic disease, and diabetes mellitus.

There are chapters on renal and ureteral injury in pregnancy, renal insufficiency from blood transfusion, and renal contraindications to pregnancy.

The book is well organized and profusely illustrated, and has a bibliography at the end of each chapter. It is indeed a scholarly treatise and deserves preëminence as a source book in the field. L. La T.

NEW BOOKS

Backache and Sciatic Neuritis. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Attending Orthopedic Surgeon, Cook County Hospital; Attending Orthopedic Surgeon, Michael Reese Hospital; Professor, Orthopedic Surgery, Cook County Graduate School of Medicine, Chicago; Lieutenant Colonel, Medical Corps, U. S. Army. Pp. 745; 235 figs. Philadelphia: Lea & Febiger, 1943. Price, $10.00.

A Hundred Years of Medicine. By C. D. HAAGENSEN and WYNDHAM E. B. LLOYD. Pp. 444; a few figs. New York: Sheridan House, 1943. Price, $3.75.

Psychosomatic Diagnosis. By FLANDERS DUNBAR, M.D., MED.Sc.D., PH.D., Department of Medicine and Psychiatry, Columbia University. Foreword by LEONARD G. ROWNTREE, Colonel, Medical Reserve Corps, U. S. Army. Pp. 741; no figs. New York, London: Paul B. Hoeber, Inc., 1943. Price, $7.50.

Medical Radiographic Technic. Edited by GLENN W. FILES, Director of General Electric *X*-Ray Corporation Technical Service Department. Pp. 365; 381 figs. Springfield: Charles C Thomas, 1943. Price, $6.00.

The Modern Management of Colitis. By J. ARNOLD BARGEN, M.D., M.S., F.A.C.P., Chief of the Section on Internal Diseases, Division of Medicine, Mayo Clinic; Associate Professor of Medicine, Mayo Foundation, Rochester, Minn.; Secretary, American Gastroenterological Association; Vice-Chairman, Section on Gastroenterology and Proctology, American Medical Association. Pp. 332; 148 figs. Springfield: Charles C Thomas, 1943. Price, $7.00.

The Arthropathies. A Handbook of Roentgen Diagnosis. By ALFRED A. DE LORIMER, A.B., M.A., M.D., Colonel, Medical Corps, U. S. Army; Commandant, The Army School of Roentgenology, Memphis, Tenn.; Formerly Director, Department of Roentgenology, Army Medical School, Washington, D. C. Pp. 319; 678 figs. Chicago: The Year Book Publishers, Inc., 1943. Price, $5.50.

Medical Parasitology and Zoölogy. By RALPH WELTY NAUSS, B.Sc., M.D., DR.P.H., Assistant Professor of Public Health and Preventive Medicine, Cornell University Medical College; Consulting Parasitologist, New York Hospital; Fellow, American Public Health Association; Lieutenant Colonel and Flight Surgeon, Medical Reserve Corps, U. S. Army. Foreword by JOHN C. TORREY, PH.D., Professor (Emeritus) of Epidemiology, Cornell University Medical College. Pp. 534; 95 figs. New York, London: Paul B. Hoeber, Inc., 1943. Price, $6.00.

A Manual of Medical Parasitology. By CLAY G HUFF, Professor of Parasitology, University of Chicago. Pp. 88; 10 plates. Chicago: University of Chicago Press, 1943. Price, $1.50.

Nelson Loose-Leaf Renewal Pages—Specialties in Medical Practice. Edited by EDGAR VAN NUYS ALLEN, M.D., Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, Minn.; Associate Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Two Vols. Pp. 270; new front matter; 2 new color plates; revised and enlarged index. New York: Thomas Nelson & Sons, 1943.

A SERIES of revised monographs by specialists bringing such information in their respective fields, as set forth in the first edition of Specialties in Medical Practice, published in 1940, up to date. There is added to this first set of Renewal Pages an article on Minor Surgery by W. Kenneth Jennings, Pittsfield, and a revision of the article on Orthopedic Surgery, with new sections and illustrations, by Don King, San Francisco. These additions, revisions of 9 other chapters, and an enlarged index, make the 1943 edition of Specialties in Medical Practice especially valuable to the physician during the busy days of war-time conditions. R. K.

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We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

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We desire to secure several copies of the March and May 1943 numbers of this Journal, in order to comply with requests and need for replacements in long library "runs." The war situation has made it impossible to print extra numbers to supply this demand. We would be *very* grateful to anyone who would return to the Publishers any unmutilated copies of these numbers for which they have no further use, and we would be glad to repay postage.